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(54) **METHODS FOR TREATMENT SELECTION FOR CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)**

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A61K 31/4184	(2006.01)
A61K 31/496	(2006.01)
A61K 31/5025	(2006.01)
A61K 31/506	(2006.01)
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(52) **U.S. Cl.**

CPC ***A61K 31/635*** (2013.01); ***A61K 31/343*** (2013.01); ***A61K 31/40*** (2013.01); ***A61K 31/4162*** (2013.01); ***A61K 31/4184*** (2013.01); ***A61K 31/496*** (2013.01); ***A61K 31/5025*** (2013.01); ***A61K 31/506*** (2013.01); ***A61K 31/519*** (2013.01); ***A61K 31/52*** (2013.01); ***A61K 45/06*** (2013.01); ***A61P 35/02*** (2018.01)

(57) **ABSTRACT**

As described below, the present invention features compositions, panels of biomarkers, and methods for selecting a subject with chronic lymphocytic leukemia (CLL) for treatment using an agent and/or for inclusion in a clinical trial using the agent to treat CLL.

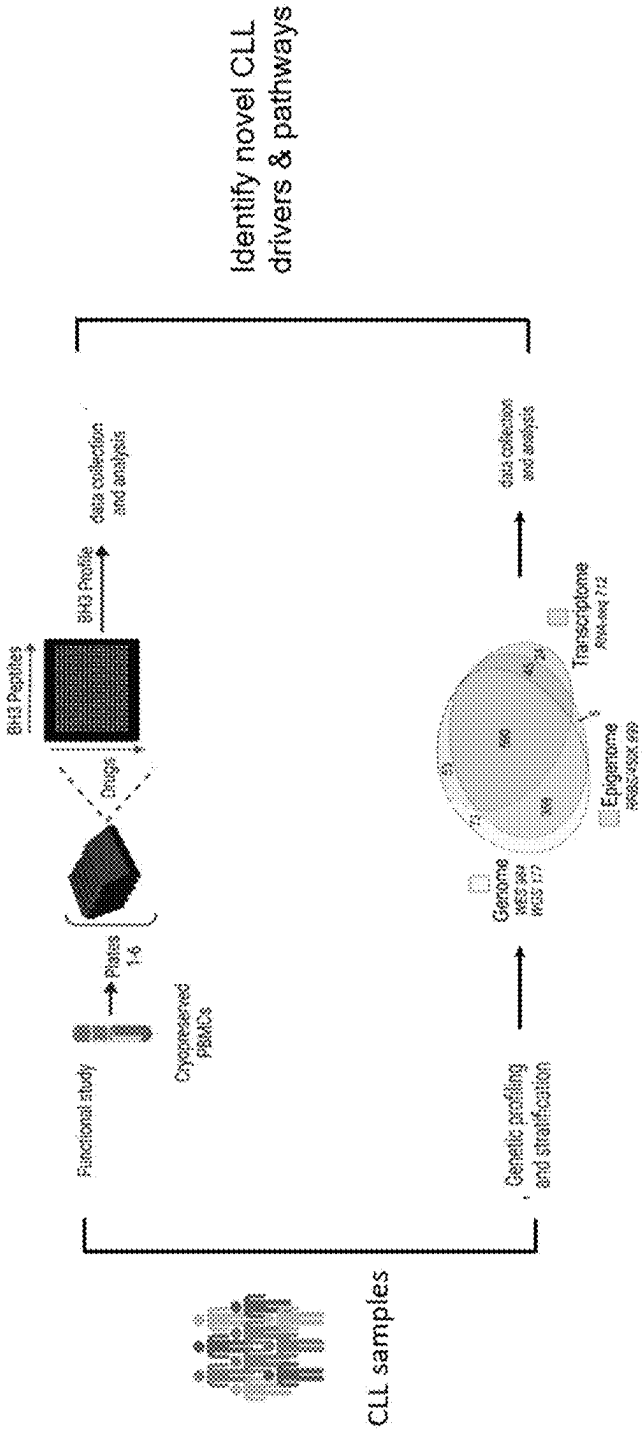
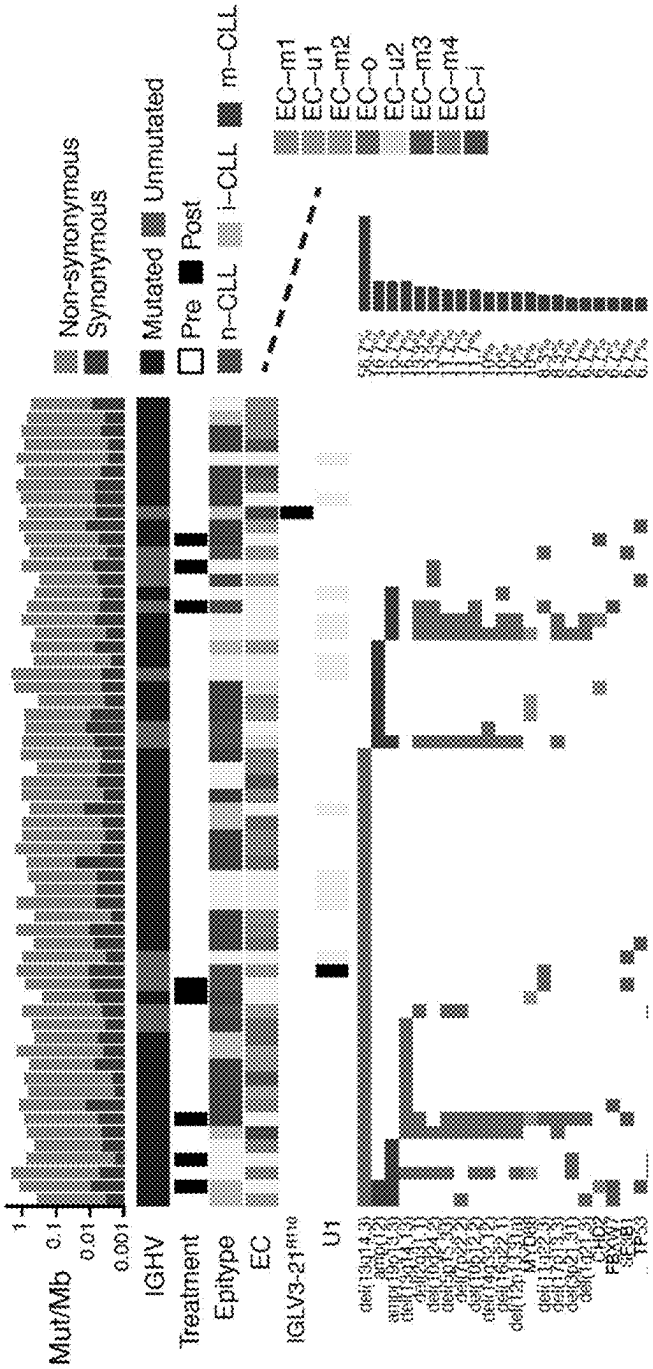
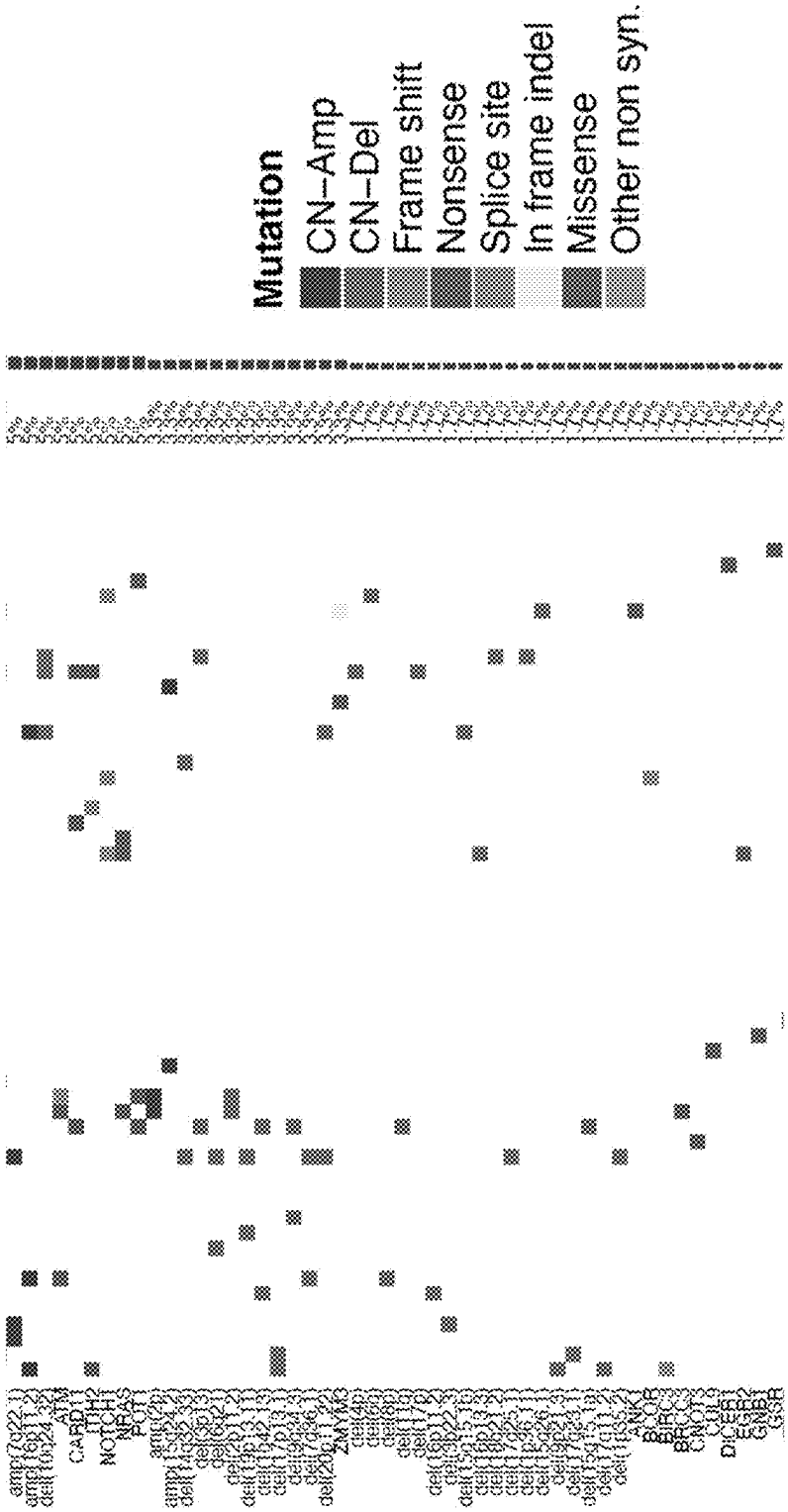

Identify novel CLL drivers & pathways
BH3 Peptides
BH3 Profile
data collection and analysis
Functional study
Plates 1-6
Cryopreserved PBMCs
Dosage
data collection and analysis
Transcriptome
Epigenome
Genome
Genetic profiling and stratification
CLL samples

FIG. 1


Non-synonymous
Synonymous
Mutated
Unmutated
Pre
Post
n-CLL
i-CLL
m-CLL
EC-m1
EC-u1
EC-m2
EC-o
EC-u2
EC-m3
EC-m4
EC-i
Mut/Mb
1
0.1
0.01
0.001
IGHV
Treatment
Epitype
EC
IGLV3-21
U1
del(13q14.3)
del(11q22.3)
del(17p13.1)
del(11q23.3)
del(6q21)
del(6q21.3)
del(6q21.1)
del(6q21.2)
del(6q21.3)
del(6q21.1)
del(6q21.2)
del(6q21.3)
del(6q21.1)
del(6q21.2


Mutation
CN–Amp
CN–Del
Frame shift
Nonsense
Splice site
In frame indel
Missense
Other non syn.
amp7q22.1
amp16p11.2
del10p14.32
ATM
CARD11
TP53
NOTCH1
NF1
RB1
amp1q32.3
amp1p36.33
del1p36.32
del3p21.31
del3p14.2
del3p13
del3p12.3
del3p12.1
del3q26.1
del3q29
del4q12
del4q13.3
del4q21.23
del4q24
del4q28.3
del4q31.21
del4q32.1
del5q11.2
del5q14.3
del5q15
del5q21.3
del5q22.2
del5q31.2
del5q32
del6q12
del6q16.3
del6q21
del6q22.33
del6q23.3
del6q24.1
del6q25.3
del6q26
del7p22.1
del7p21.3
del7q11.23
del7q21.11
del7q31.1
del7q31.31
del7q32.1
del7q36.1
del8p12
del8p21.2
del8p23.1
del8q11.21
del8q12.1
del8q21.11
del8q21.13
del8q22.1
del8q22.3
del8q23.1
del8q24.21
del8q24.22
del8q24.23
del8q24.3
del9p21.3
del9p21.33
del9q21.11
del9q22.32
del9q33.3
del9q34.11
del9q34.12
del9q34.13
del9q34.2
del9q34.3
del10q23.31
del10q23.33
del10q24.32
del11q13.2
del11q13.3
del11q14.1
del11q22.3
del11q23.3
del11q24.3
del11q25
del12q13.13
del12q14.1
del12q15
del12q21.31
del12q24.31
del13q12.11
del13q14.11
del13q14.2
del13q14.3
del13q21.1
del13q21.33
del13q22.1
del13q31.1
del13q31.3
del13q32.1
del13q34
del14q32.33
del15q11.2
del15q13.1
del15q15.1
del15q21.1
del15q21.2
del15q21.3
del15q22.31
del15q22.33
del15q23
del15q24.1
del15q24.2
del15q25.1
del15q26.1
del16q23.1
del16q23.2
del16q24.1
del16q24.3
del17p13.1
del17p13.3
del17q11.2
del17q12
del17q21.31
del17q21.32
del17q23.1
del17q23.2
del17q24.3
del17q25.1
del17q25.3
del18q21.32
del18q22.3
del18q23
del19p13.3
del19q13.11
del19q13.12
del19q13.32
del19q13.33
del19q13.42
del19q13.43
del20q11.22
del20q13.12
del20q13.13
del20q13.33
del21q22.3
del22q11.21
del22q11.23
del22q12.1
del22q12.3
del22q13.1
del22q13.2
del22q13.3
del22q13.31
del22q13.32
del22q13.33
del22q13.34
del22q13.35
del22q13.36
del22q13.37
del22q13.38
del22q13.39
del22q13.40
del22q13.41
del22q13.42
del22q13.43
del22q13.44
del22q13.45
del22q13.46
del22q13.47
del22q13.48
del22q13.49
del22q13.50
del22q13.51
del22q13.52
del22q13.53
del22q13.54
del22q13.55
del22q13.56
del22q13.57
del22q13.58
del22q13.59
del22q13.60
del22q13.61
del22q13.62
del22q13.63
del22q13.64
del22q13.65
del22q13.66
del22q13.67
del22q13.68
del22q13.69

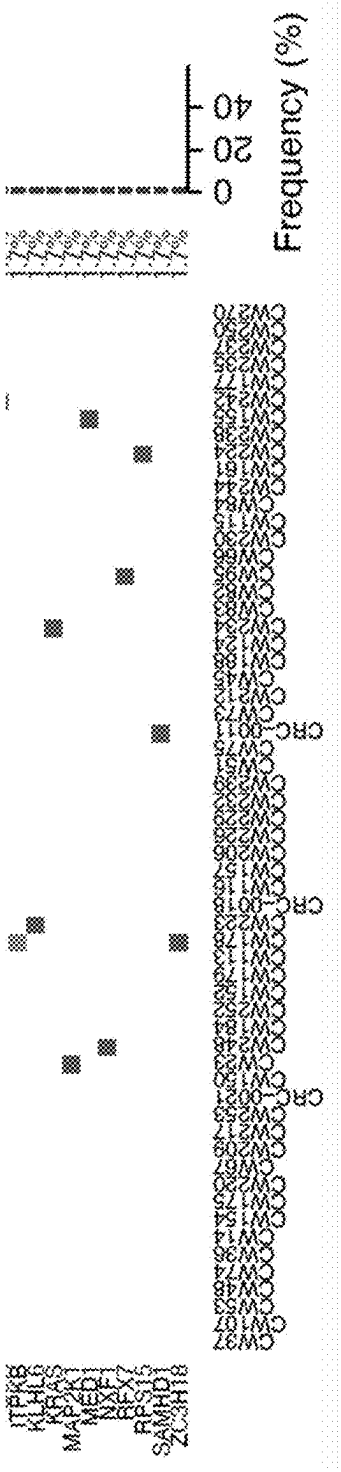


FIG. 2A (Continued)

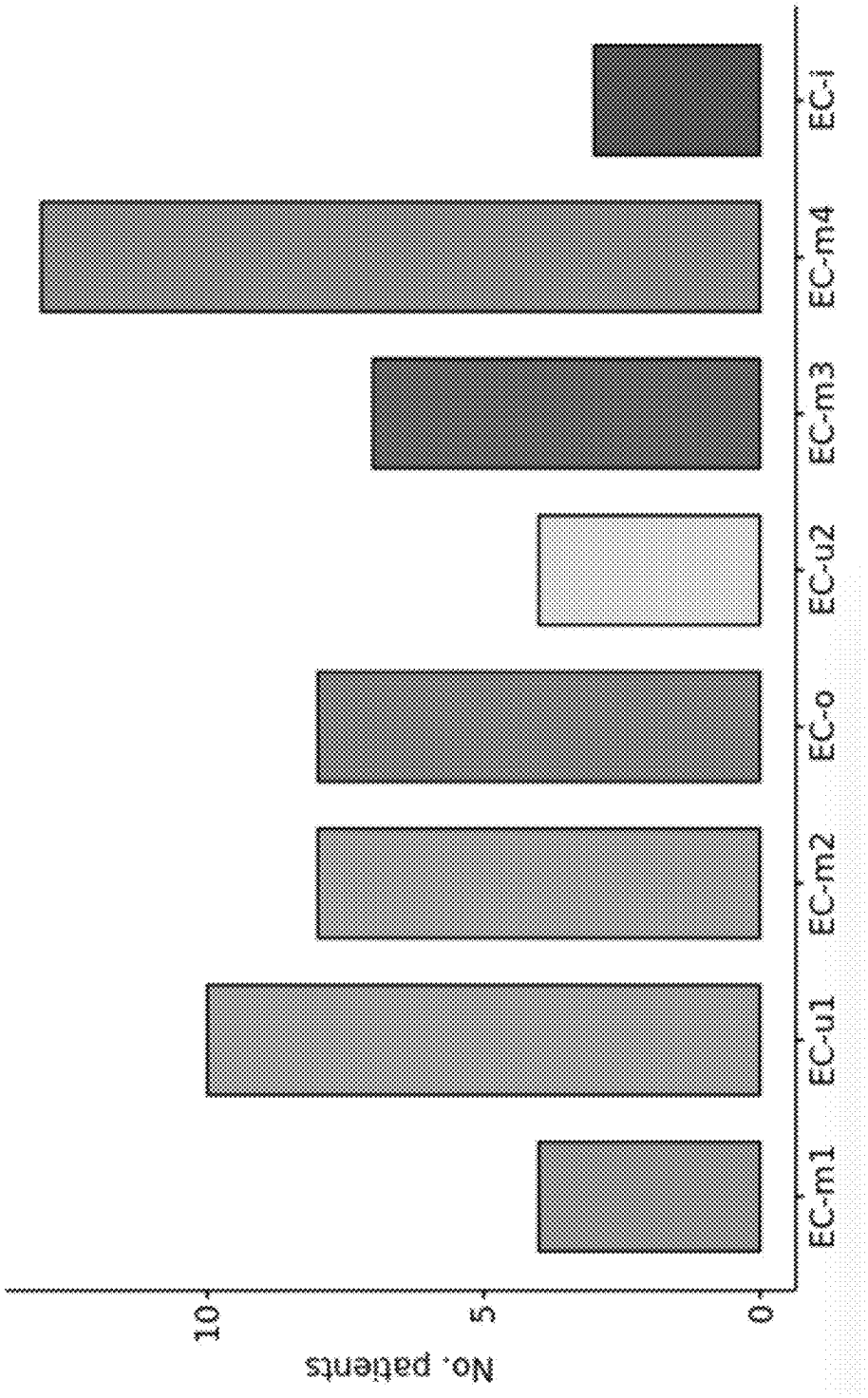


FIG. 2B

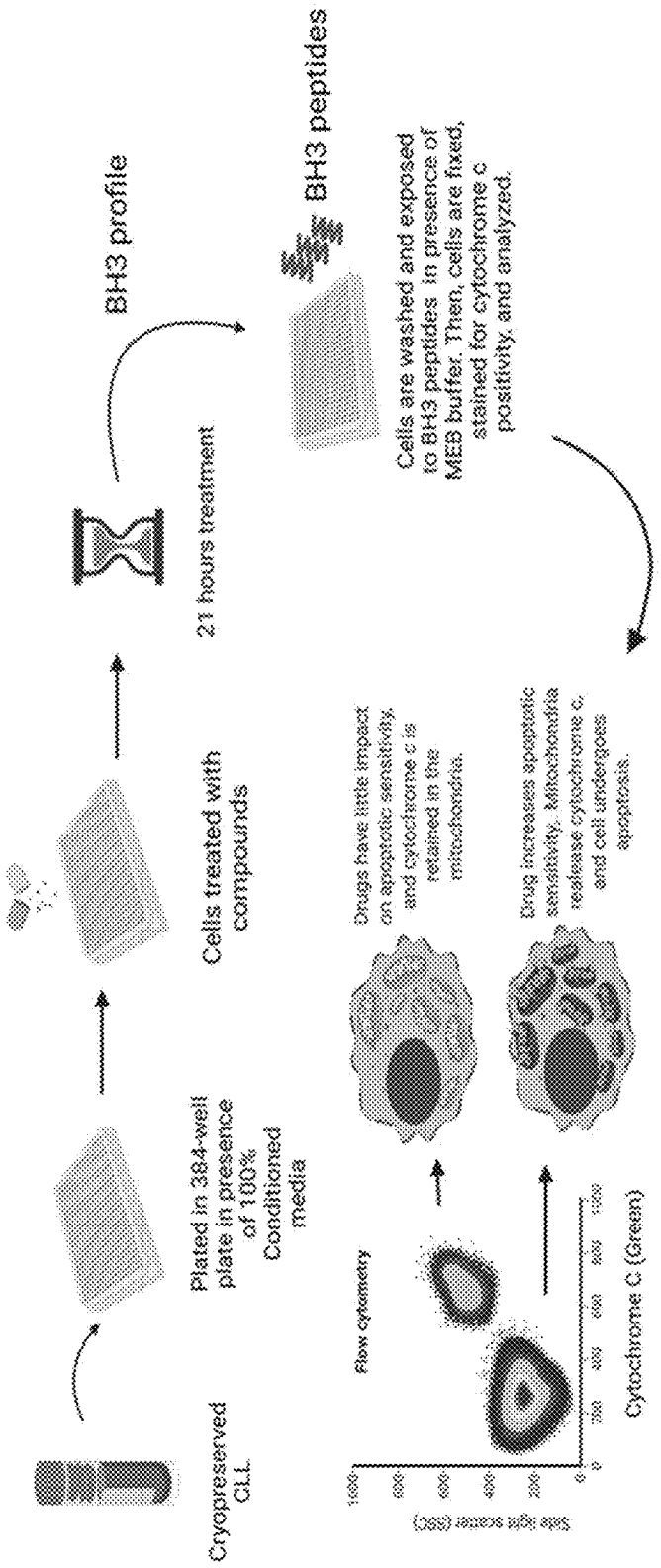

Cryopreserved CLL
Plated in 384-well plate in presence of 100% Conditioned media
Cells treated with compounds
21 hours treatment
BH3 profile
BH3 peptides
Cells are washed and exposed to BH3 peptides in presence of MEB buffer. Then, cells are fixed, stained for cytochrome c positivity, and analyzed.
Flow cytometry
Drugs have little impact on apoptotic sensitivity, and cytochrome c is retained in the mitochondria.
Drug increases apoptotic sensitivity. Mitochondria release cytochrome c, and cell undergoes apoptosis.
Side light scatter (SSC)
Cytochrome C (Green)

FIG. 3

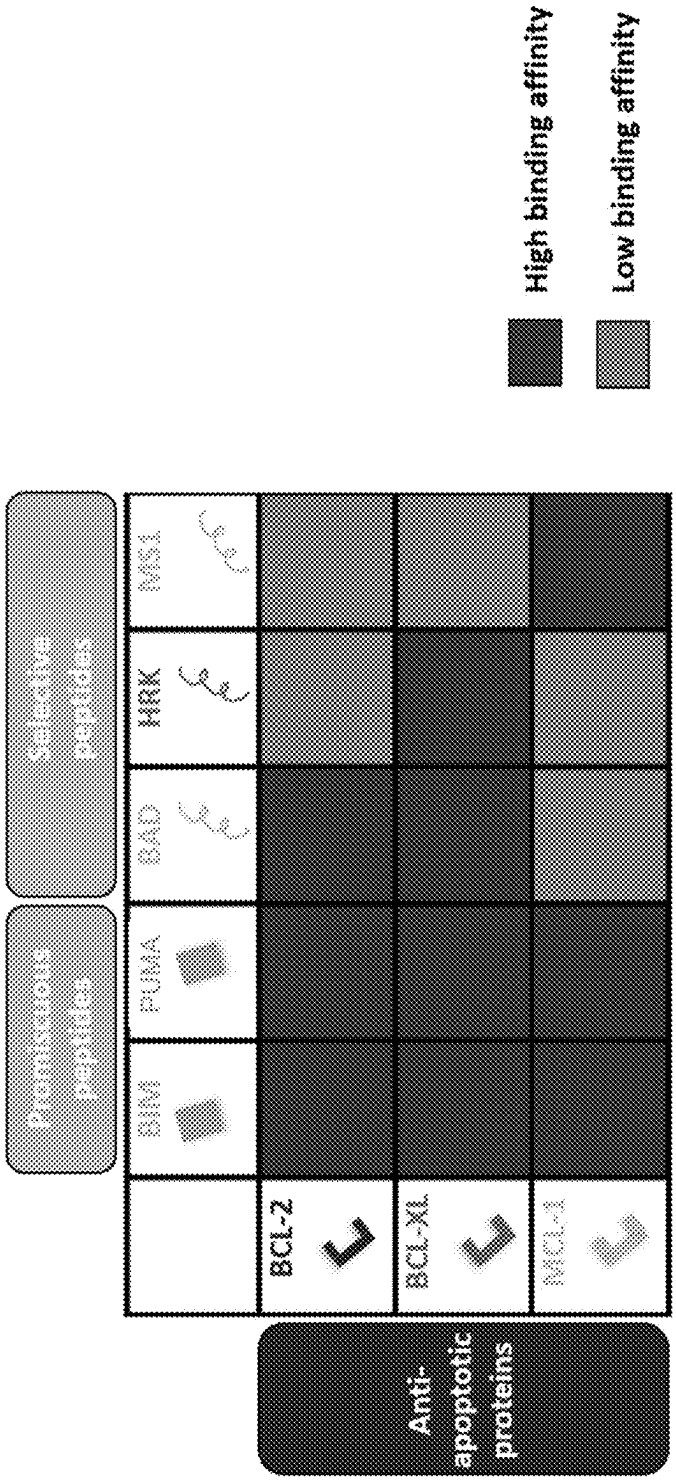

Pro-apoptotic Peptides
Sensitizer Peptides
BIM
PUMA
BAD
HRK
MS1
BCL-2
BCL-XL
MCL-1
Anti-apoptotic proteins
High binding affinity
Low binding affinity

FIG. 4

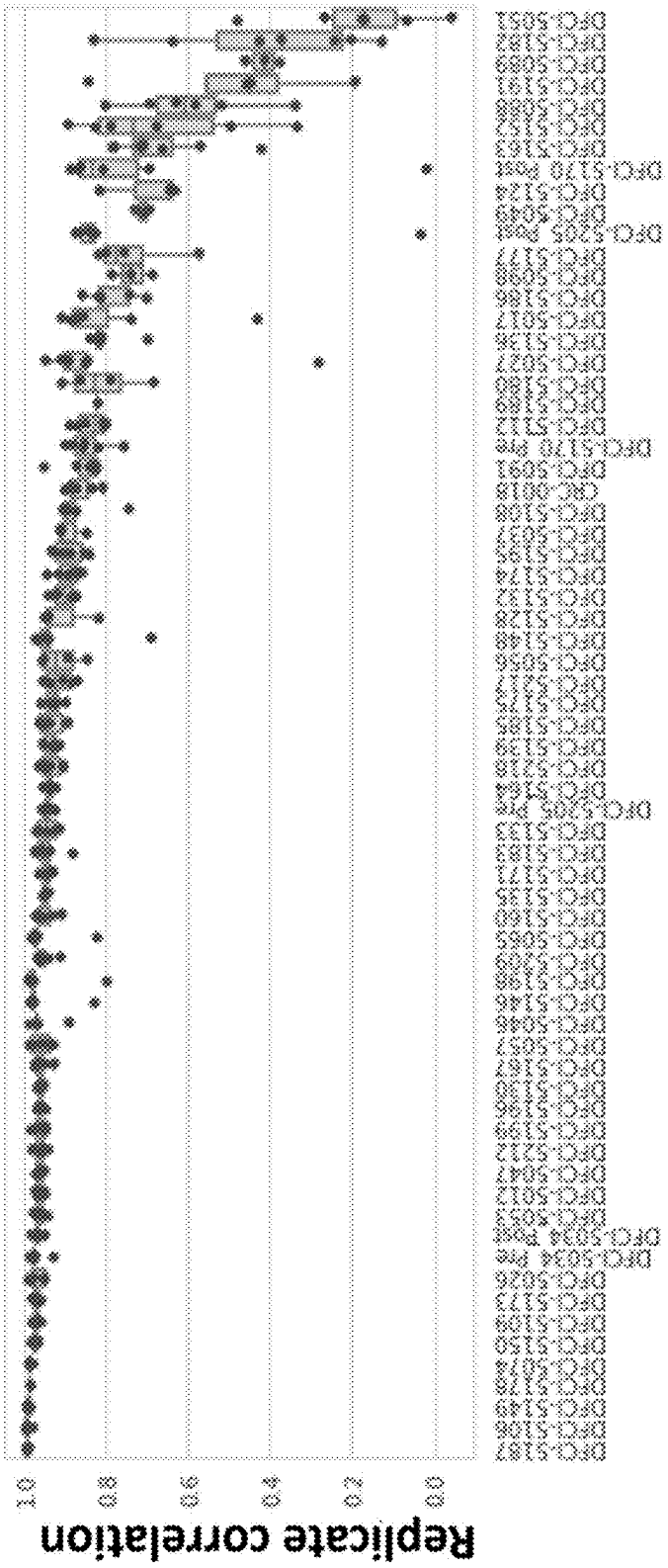

Replicate correlation
1.0
0.8
0.6
0.4
0.2
0.0
DFCL5187
DFCL5146
DFCL5148
DFCL5178
DFCL5174
DFCL5150
DFCL5108
DFCL5173
DFCL5026
DFCL5034 Pre
DFCL5034 Post
DFCL5057
DFCL5015
DFCL5047
DFCL5212
DFCL5198
DFCL5195
DFCL5192
DFCL5193
DFCL5146
DFCL5046
DFCL5065
DFCL5163
DFCL5155
DFCL5165
DFCL5065
DFCL5207
DFCL5168
DFCL5171
DFCL5155
DFCL5161
DFCL5153
DFCL5206 Pre
DFCL5128
DFCL5148
DFCL5056
DFCL5176
DFCL5174
DFCL5185
DFCL5135
DFCL5178
DFCL5184
DFCL5206 Post
DFCL5123
DFCL5161
DFCL5171
DFCL5155
DFCL5160
DFCL5065
DFCL5207
DFCL5168
DFCL5146
DFCL5046
DFCL5065
DFCL5163
DFCL5212
DFCL5198
DFCL5195
DFCL5192
DFCL5047
DFCL5015
DFCL5057
DFCL5034 Post
DFCL5034 Pre
DFCL5026
DFCL5173
DFCL5108
DFCL5150
DFCL5174
DFCL5178
DFCL5148
DFCL5106
DFCL5187
DFCL5051
DFCL5182
DFCL5089
DFCL5191
DFCL5202
DFCL5152
DFCL5153
DFCL5170 Post
DFCL5124
DFCL5048
DFCL5205 Post
DFCL5149
DFCL5099
DFCL5196
DFCL5017
DFCL5138
DFCL5027
DFCL5189
DFCL5169
DFCL5112
DFCL5170 Pre
DFCL5091
CDC-0018
DFCL5108
DFCL5152
DFCL5165
DFCL5174
DFCL5155
DFCL5128
DFCL5148
DFCL5056
DFCL5176
DFCL5174
DFCL5185
DFCL5135
DFCL5178
DFCL5184
DFCL5206 Pre
DFCL5123

FIG. 5A

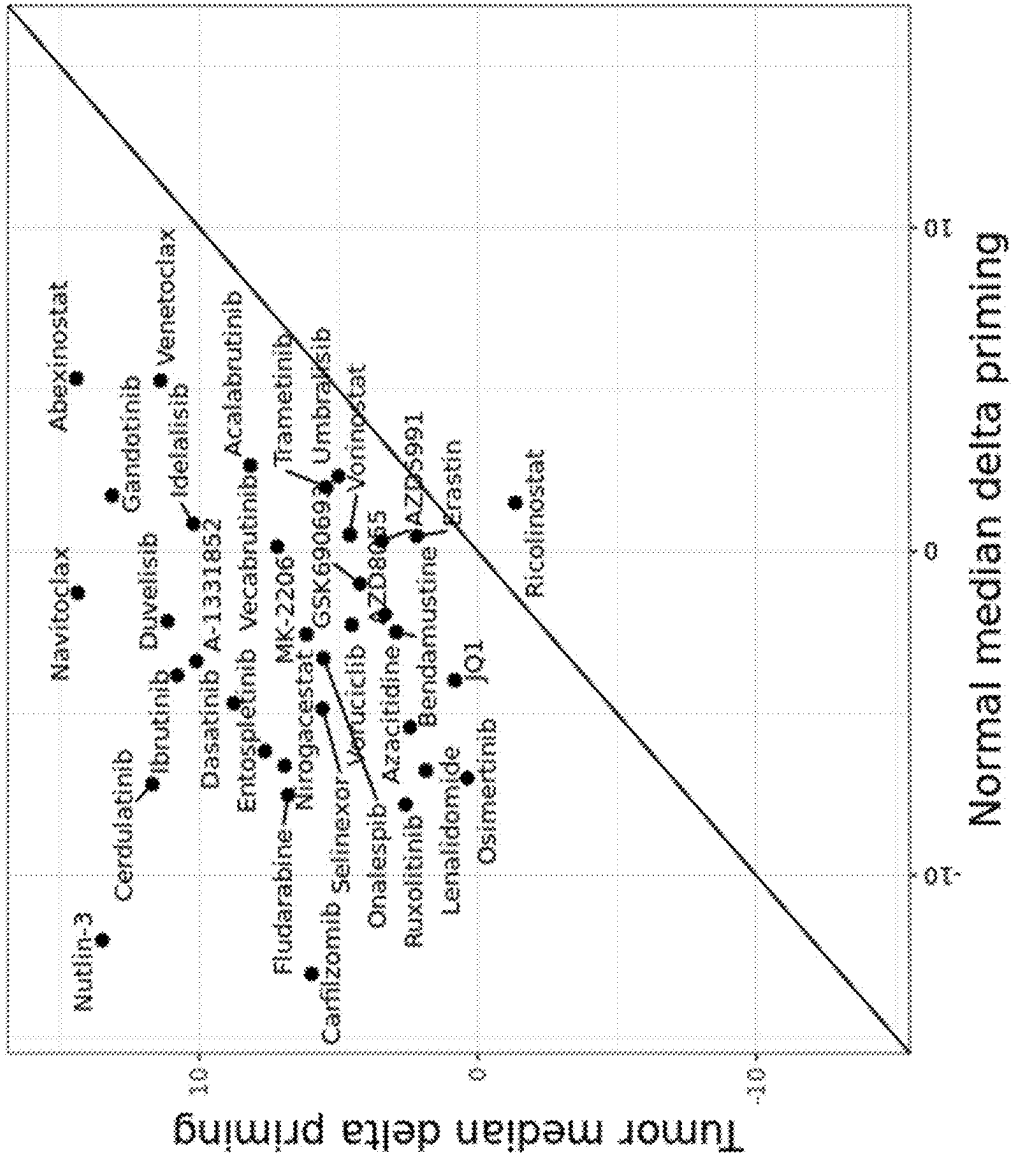

Tumor median delta priming
Normal median delta priming
10
0
-10
Abexinostat
Venetoclax
Gandotinib
Idelalisib
Navitoclax
Duvelisib
A-133852
Acalabrutinib
Trametinib
Umbralisib
Vorinostat
Vecabrutinib
MK-2206
GSK690693
AZD8055
AZD5991
Erastin
Ibrutinib
Dasatinib
Entospletinib
Nitrogacestat
Selinexor
Verdiciclib
Azacitidine
Bendamustine
JQ1
Ricolinostat
Cerdulatinib
Fludarabine
Carfilzomib
Onalespib
Ruxolitinib
Lenalidomide
Osimertinib
Nutlin-3

FIG. 5B

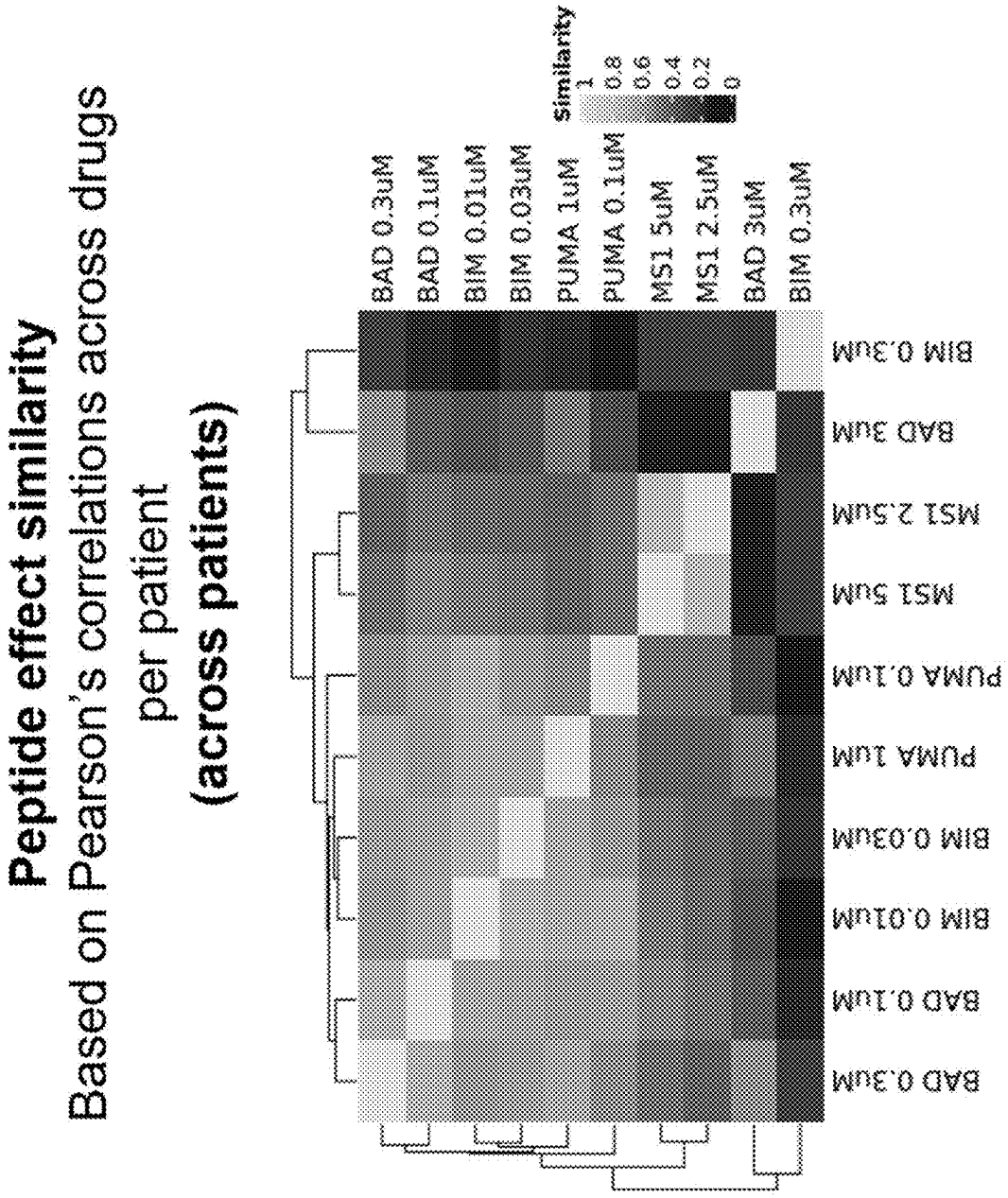

Peptide effect similarity
Based on Pearson's correlations across drugs
per patient
(across patients)
BAD 0.3uM
BAD 0.1uM
BIM 0.01uM
BIM 0.03uM
PUMA 1uM
PUMA 0.1uM
MS1 5uM
MS1 2.5uM
BAD 3uM
BIM 0.3uM
Similarity
1
0.8
0.6
0.4
0.2
0
BAD 0.3uM
BAD 0.1uM
BIM 0.01uM
BIM 0.03uM
PUMA 1uM
PUMA 0.1uM
MS1 5uM
MS1 2.5uM
BAD 3uM
BIM 0.3uM

FIG. 6A

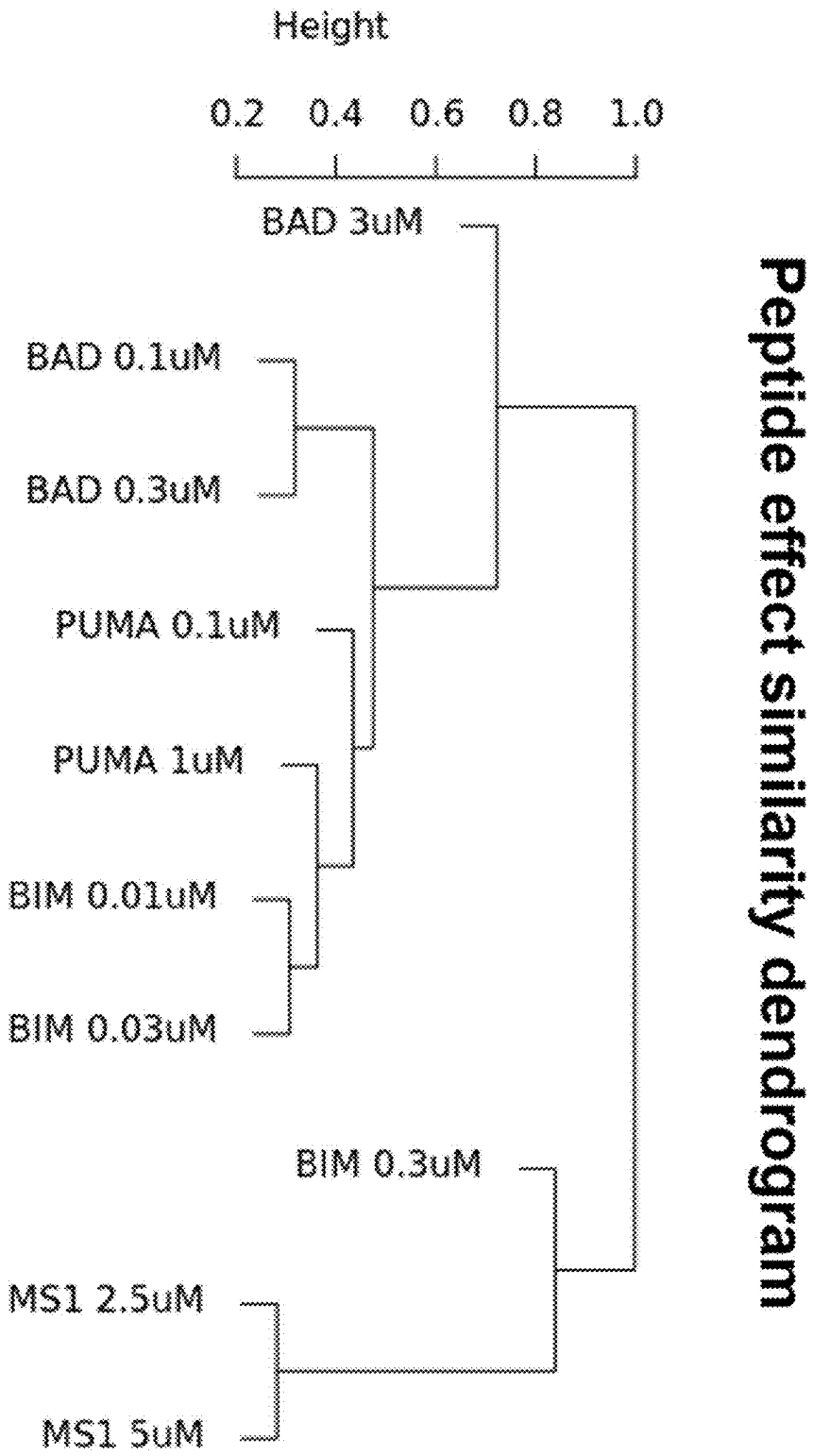

Peptide effect similarity dendrogram
Height
0.2
0.4
0.6
0.8
1.0
BAD 3uM
BAD 0.1uM
BAD 0.3uM
PUMA 0.1uM
PUMA 1uM
BIM 0.01uM
BIM 0.03uM
BIM 0.3uM
MS1 2.5uM
MS1 5uM

FIG. 6B

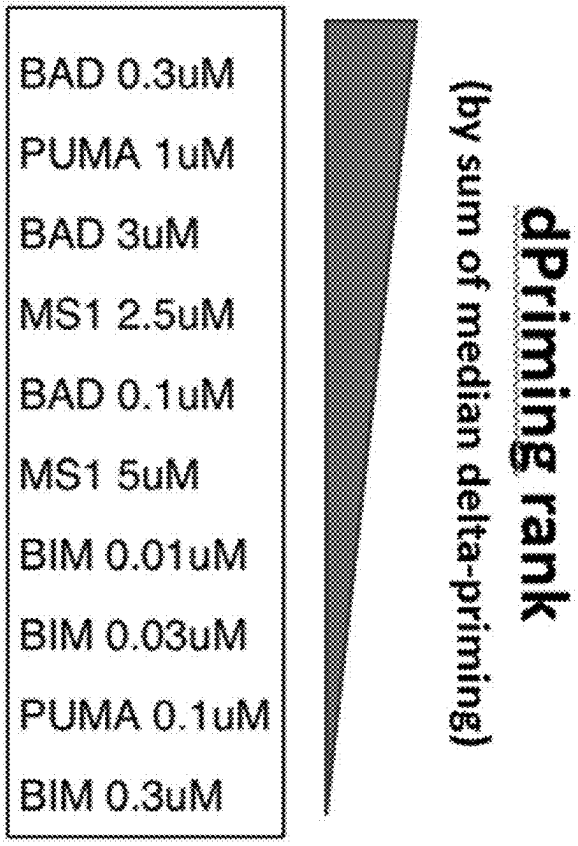

dPriming rank
(by sum of median delta-priming)
BAD 0.3uM
PUMA 1uM
BAD 3uM
MS1 2.5uM
BAD 0.1uM
MS1 5uM
BIM 0.01uM
BIM 0.03uM
PUMA 0.1uM
BIM 0.3uM

FIG. 7A

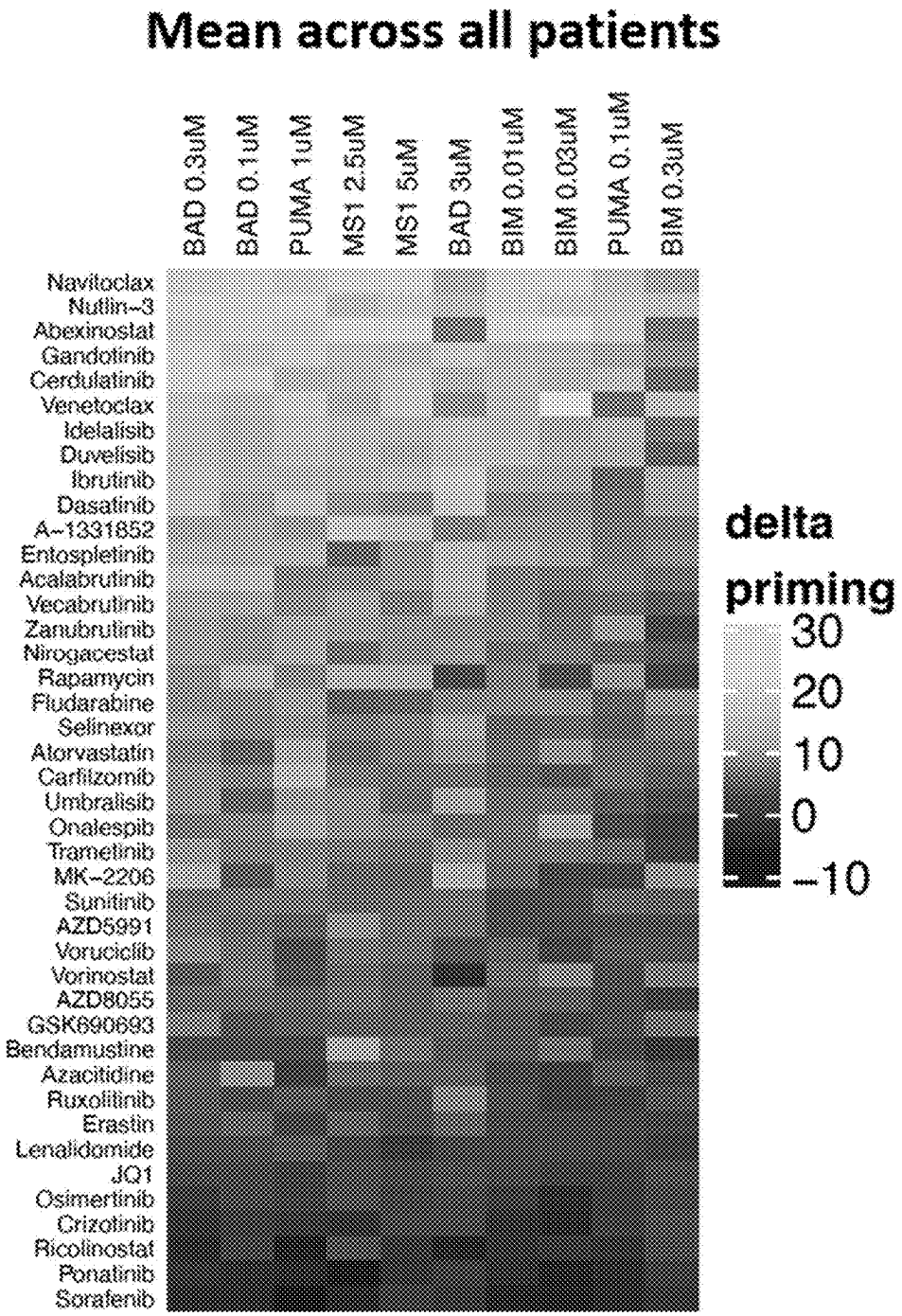

Mean across all patients
BAD 0.3uM
BAD 0.1uM
PUMA 1uM
MS1 2.5uM
MS1 5uM
BAD 3uM
BIM 0.01uM
BIM 0.03uM
PUMA 0.1uM
BIM 0.3uM
Navitoclax
Nutlin-3
Abexinostat
Gandotinib
Cerdulatinib
Venetoclax
Idelalisib
Duvelisib
Ibrutinib
Dasatinib
A-1331852
Entospletinib
Acalabrutinib
Vecabrutinib
Zanubrutinib
Nirogacestat
Rapamycin
Fludarabine
Selinexor
Atorvastatin
Carfilzomib
Umbralisib
Onalespib
Trametinib
MK-2206
Sunitinib
AZD5991
Voruciclib
Vorinostat
AZD8055
GSK690693
Bendamustine
Azacitidine
Ruxolitinib
Erastin
Lenalidomide
JQ1
Osimertinib
Crizotinib
Ricolinostat
Ponatinib
Sorafenib
delta
priming
30
20
10
0
−10

FIG. 7B

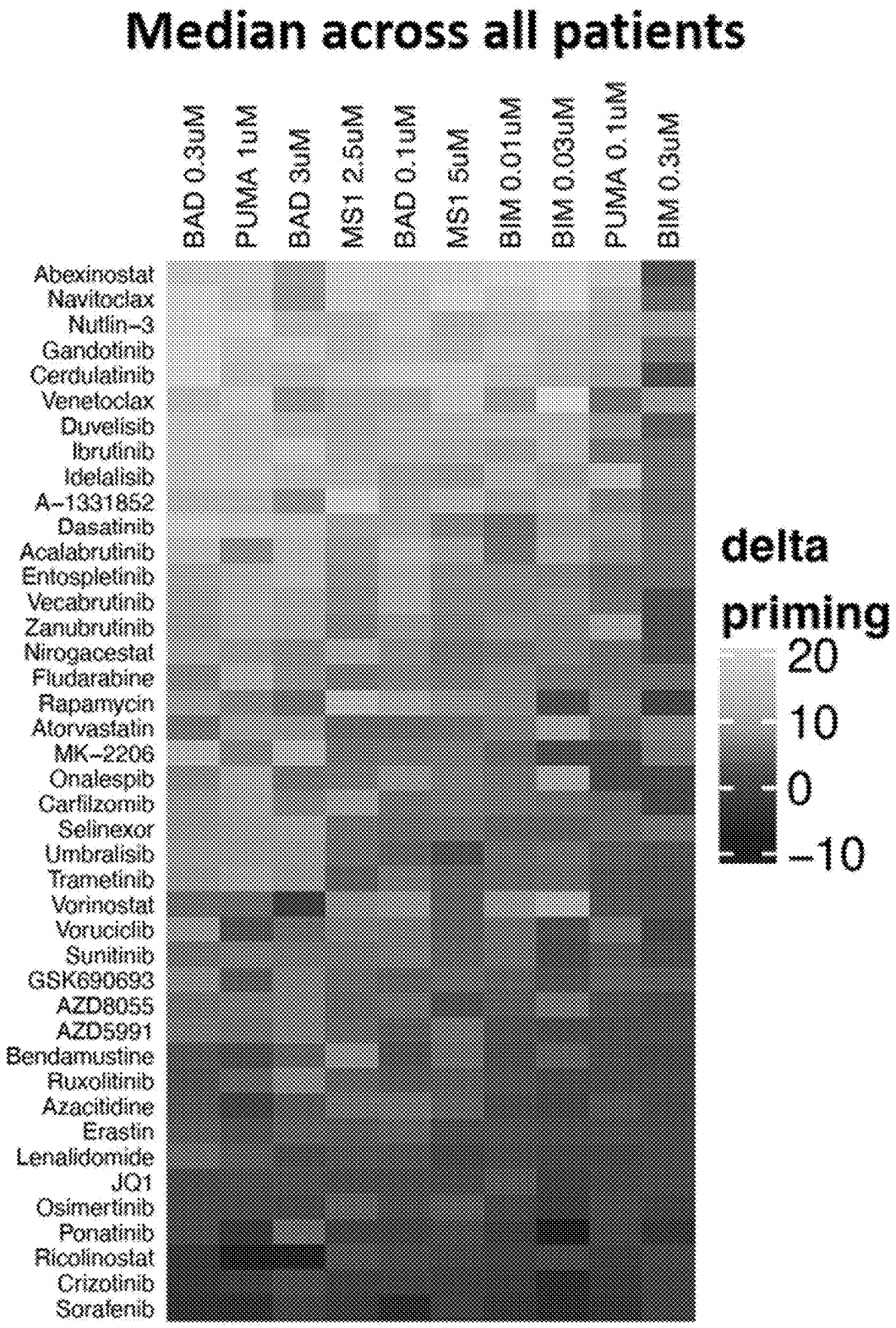

Median across all patients
BAD 0.3uM
PUMA 1uM
BAD 3uM
MS1 2.5uM
BAD 0.1uM
MS1 5uM
BIM 0.01uM
BIM 0.03uM
PUMA 0.1uM
BIM 0.3uM
Abexinostat
Navitoclax
Nutlin-3
Gandotinib
Cerdulatinib
Venetoclax
Duvelisib
Ibrutinib
Idelalisib
A-1331852
Dasatinib
Acalabrutinib
Entospletinib
Vecabrutinib
Zanubrutinib
Nirogacestat
Fludarabine
Rapamycin
Atorvastatin
MK-2206
Onalespib
Carfilzomib
Selinexor
Umbralisib
Trametinib
Vorinostat
Voruciclib
Sunitinib
GSK690693
AZD8055
AZD5991
Bendamustine
Ruxolitinib
Azacitidine
Erastin
Lenalidomide
JQ1
Osimertinib
Ponatinib
Ricolinostat
Crizotinib
Sorafenib
delta
priming
20
10
0
−10

FIG. 7C

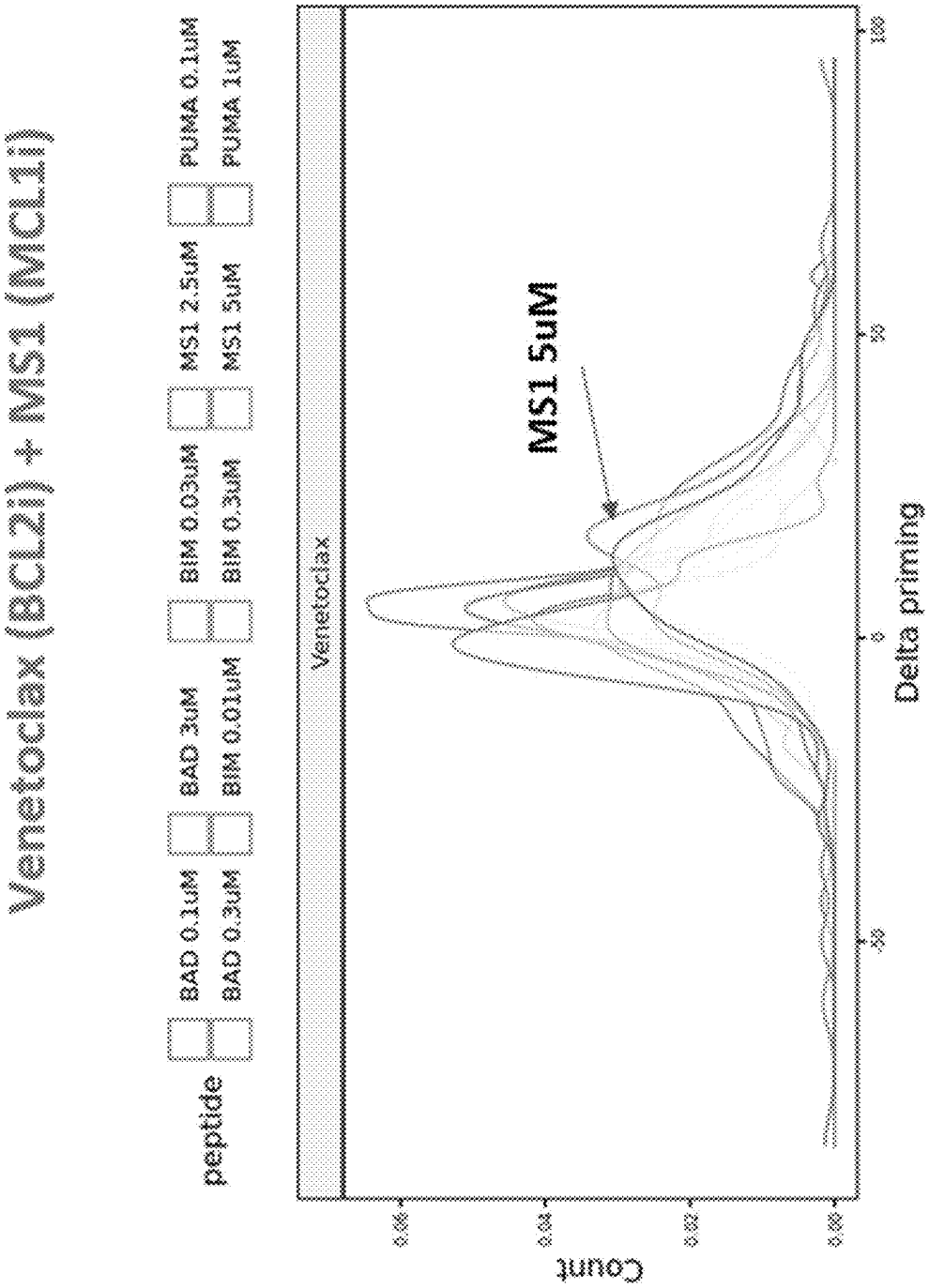

Venetoclax (BCL2i) + MS1 (MCL1i)
peptide
BAD 0.1uM
BAD 0.3uM
BAD 3uM
BIM 0.01uM
BIM 0.03uM
BIM 0.3uM
MS1 2.5uM
MS1 5uM
PUMA 0.1uM
PUMA 1uM
Venetoclax
MS1 5uM
Count
0.06
0.04
0.02
0.00
-20
0
20
100
Delta priming

FIG. 8A

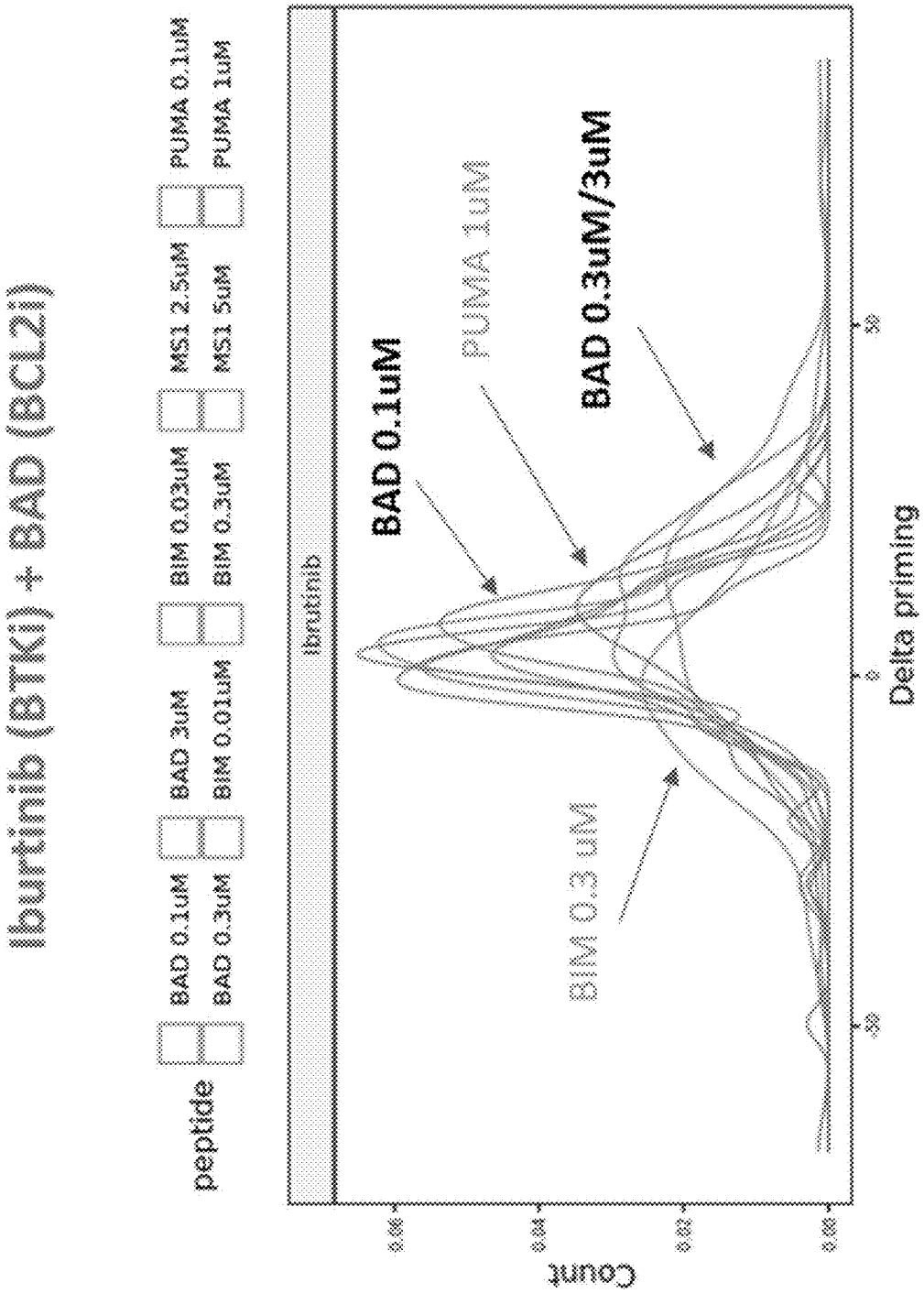

Ibrutinib (BTKi) + BAD (BCL2i)
peptide
BAD 0.1uM
BAD 0.3uM
BAD 3uM
BIM 0.01uM
BIM 0.03uM
BIM 0.3uM
MS1 2.5uM
MS1 5uM
PUMA 0.1uM
PUMA 1uM
Ibrutinib
BAD 0.1uM
PUMA 1uM
BAD 0.3uM/3uM
BIM 0.3 uM
Count
0.06
0.04
0.02
0.00
-50
0
50
Delta priming

FIG. 8B

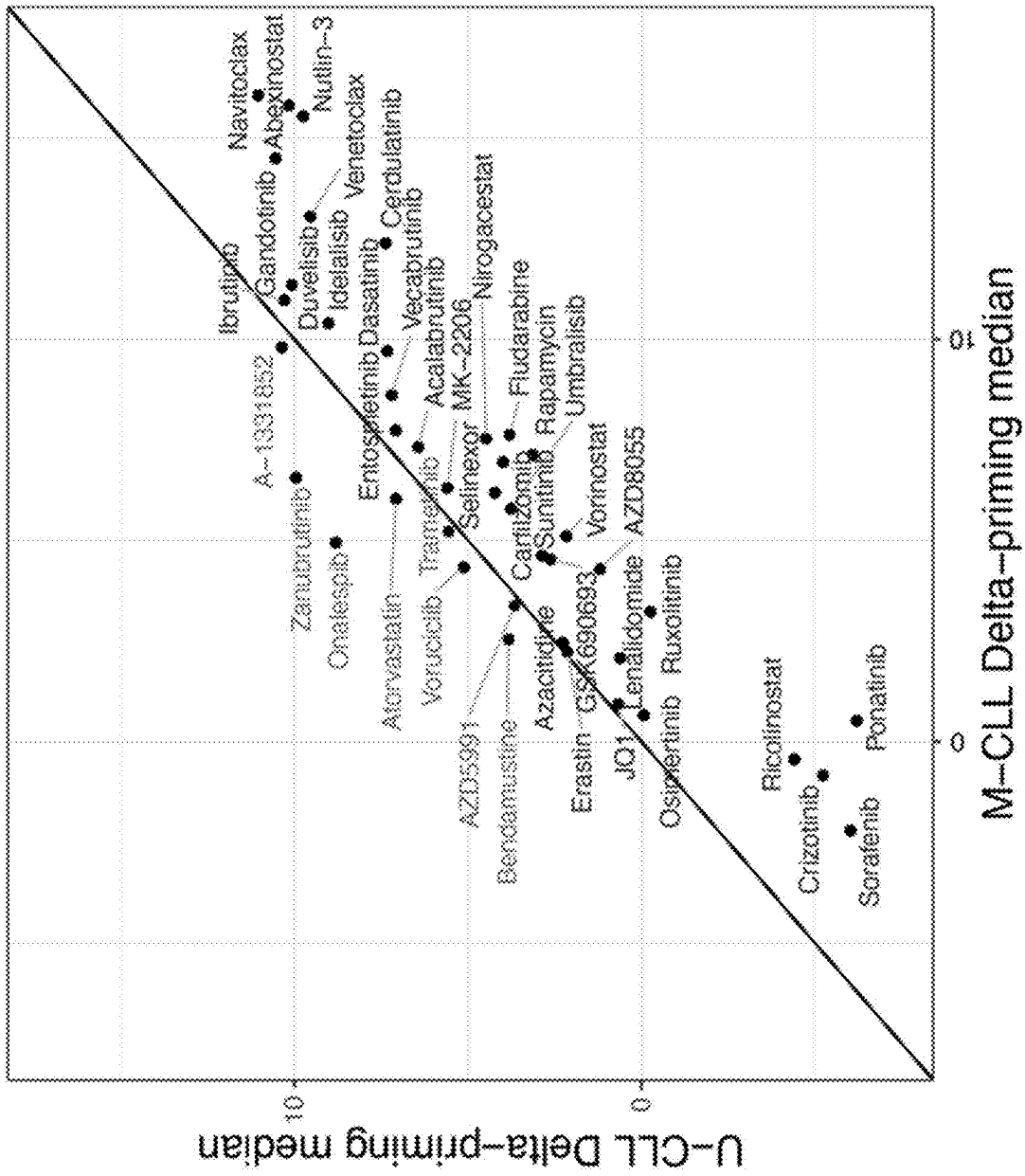

U-CLL Delta-priming median
M-CLL Delta-priming median
10
0
10
0
Navitoclax
Abexinostat
Nutlin-3
Venetoclax
Ganetespib
Duvelisib
Idelalisib
Ibrutinib
Cerdulatinib
Dasatinib
Vecabrutinib
Entospletinib
Acalabrutinib
Nirogacestat
A-1331852
MK-2206
Fludarabine
Rapamycin
Umbralisib
Zanubrutinib
Onalespib
Selinexor
Sunitinib
Vorinostat
Atorvastatin
Trametinib
Carfilzomib
AZD8055
Vorucicib
Azacitidine
Lenalidomide
Ruxolitinib
AZD5991
Bendamustine
Erastin
GSK690693
JQ1
Osimertinib
Ricolinostat
Crizotinib
Ponatinib
Sorafenib

FIG. 9

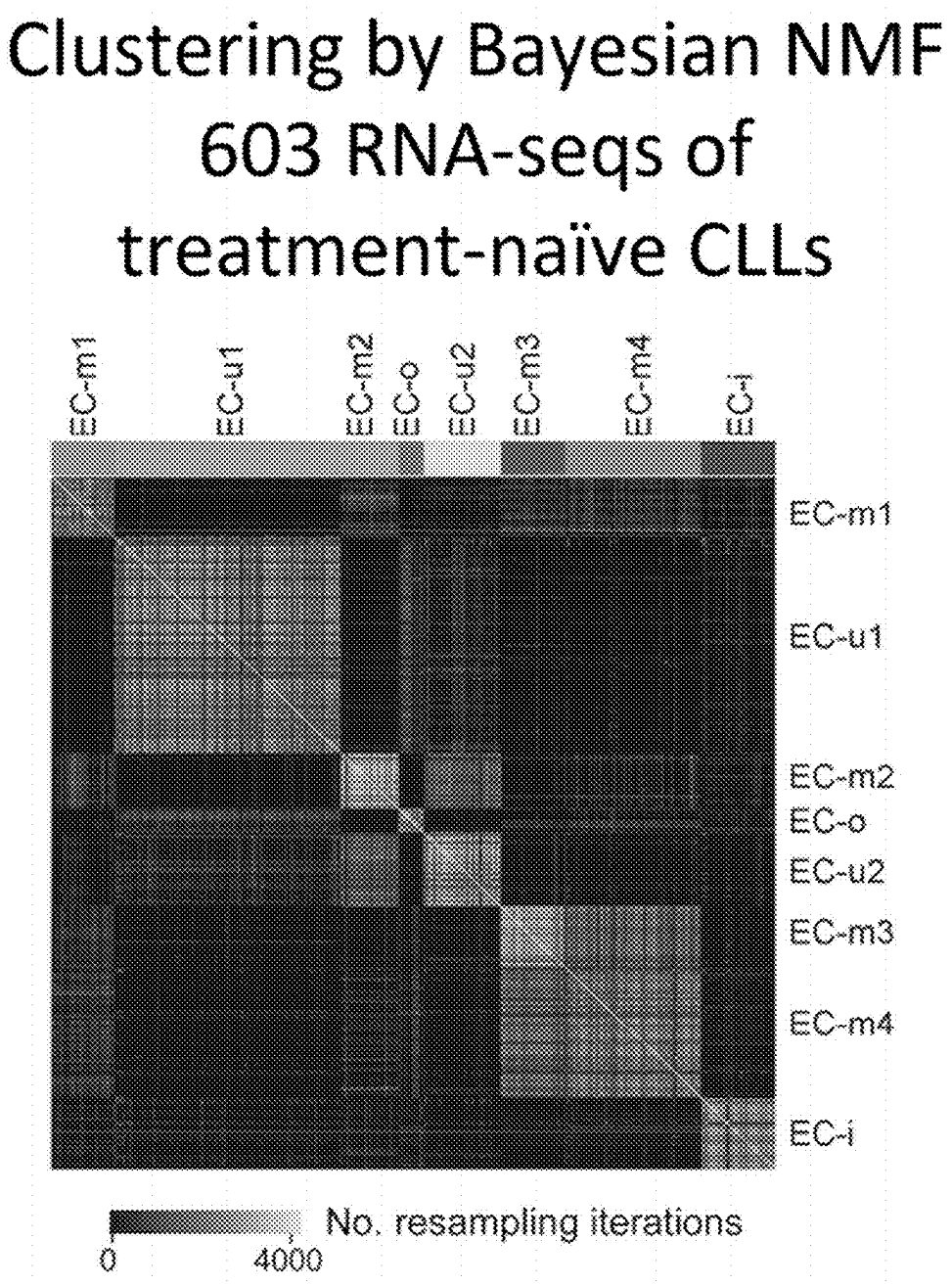

Clustering by Bayesian NMF
603 RNA-seqs of
treatment-naïve CLLs
EC-m1
EC-u1
EC-m2
EC-o
EC-u2
EC-m3
EC-m4
EC-i
No. resampling iterations
0
4000

FIG. 10A

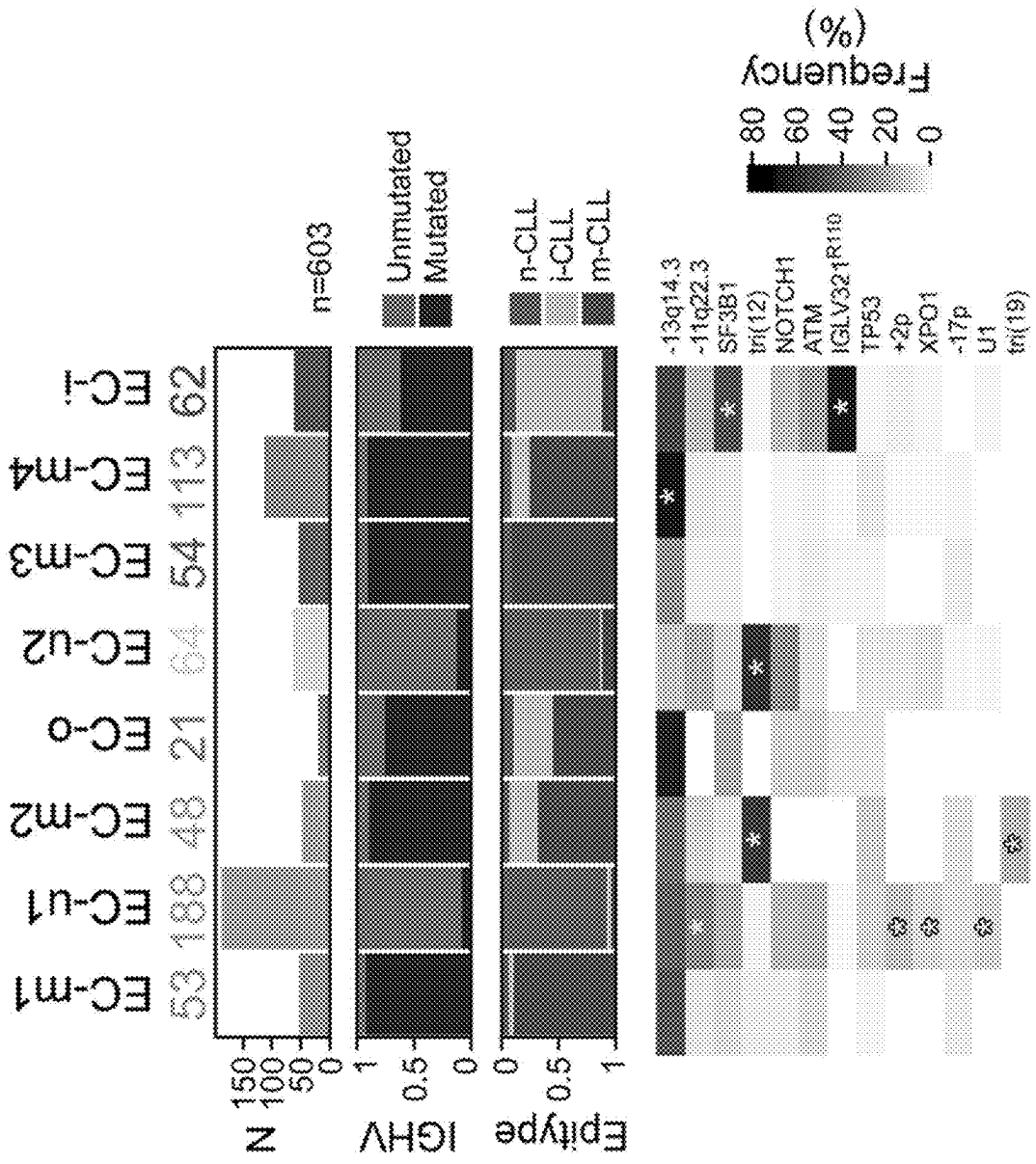

EC-m1
EC-u1
EC-m2
EC-o
EC-u2
EC-m3
EC-m4
EC-i
53
188
48
21
64
54
113
62
N
150
100
50
0
n=603
IGHV
1
0.5
0
Unmutated
Mutated
Epitype
0
0.5
1
n-CLL
i-CLL
m-CLL
-13q14.3
-11q22.3
SF3B1
tri(12)
NOTCH1
ATM
IGLV3-21R110
TP53
+2p
XPO1
-17p
U1
tri(19)
Frequency
(%)
80
60
40
20
0

FIG. 10B

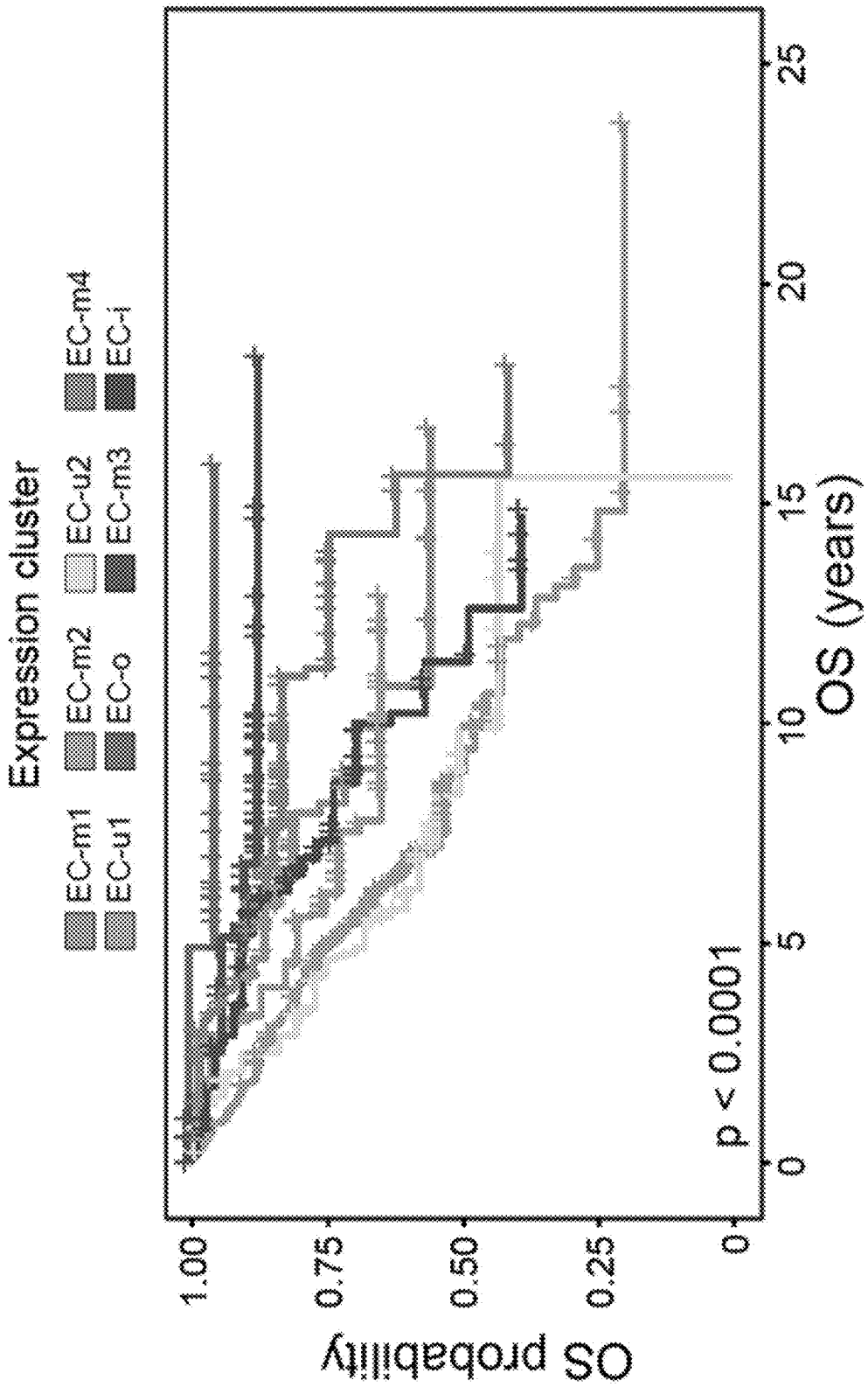

Expression cluster
EC-m1
EC-u1
EC-m2
EC-o
EC-u2
EC-m3
EC-m4
EC-i
OS probability
1.00
0.75
0.50
0.25
0
p < 0.0001
0
5
10
15
20
25
OS (years)

FIG. 10C

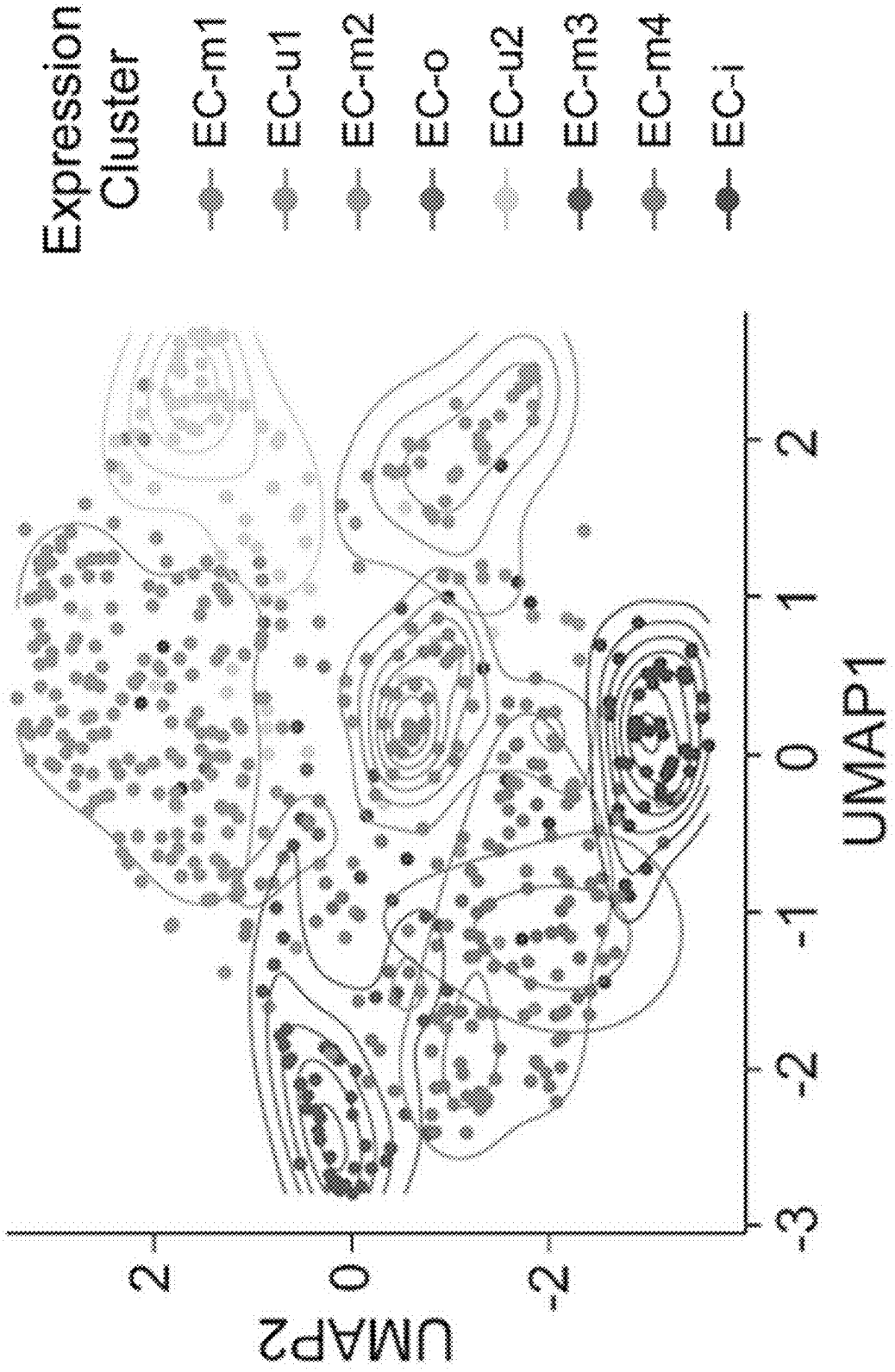

Expression Cluster
EC-m1
EC-u1
EC-m2
EC-o
EC-u2
EC-m3
EC-m4
EC-i
UMAP2
2
0
-2
UMAP1
-3
-2
-1
0
1
2

FIG. 10D

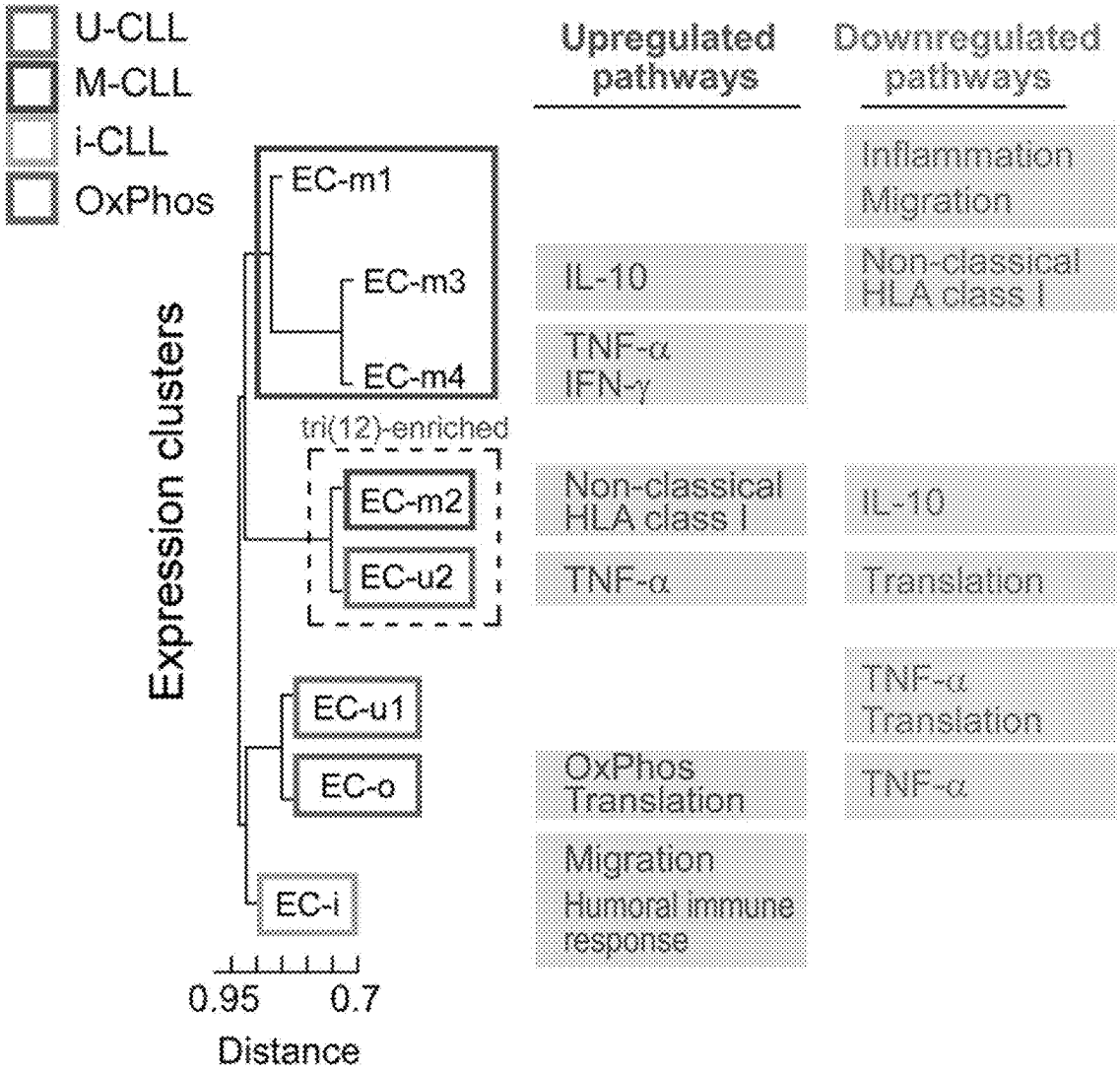

U-CLL
M-CLL
i-CLL
OxPhos
Expression clusters
EC-m1
EC-m3
EC-m4
tri(12)-enriched
EC-m2
EC-u2
EC-u1
EC-o
EC-i
0.95
0.7
Distance
Upregulated pathways
IL-10
TNF-α
IFN-γ
Non-classical HLA class I
TNF-α
OxPhos
Translation
Migration
Humoral immune response
Downregulated pathways
Inflammation
Migration
Non-classical HLA class I
IL-10
Translation
TNF-α
Translation
TNF-α

FIG. 11

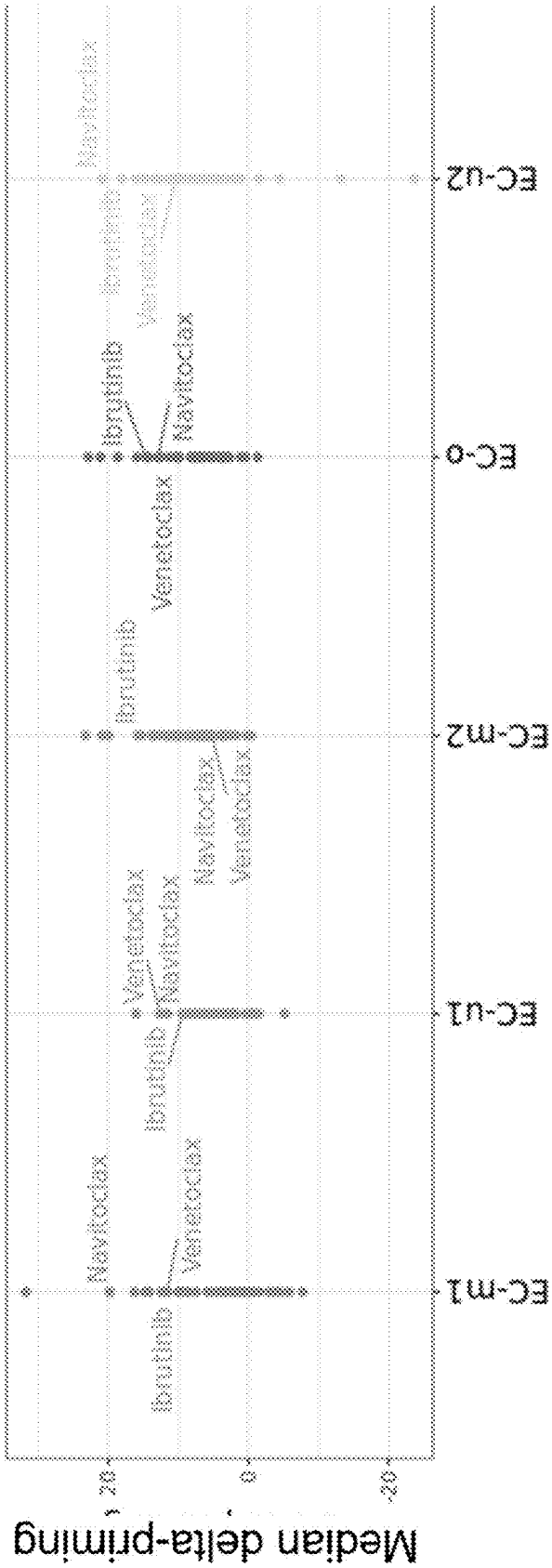

Median delta-priming
20
0
-20
EC-m1
EC-u1
EC-m2
EC-o
EC-u2
Ibrutinib
Navitoclax
Venetoclax

FIG. 12A

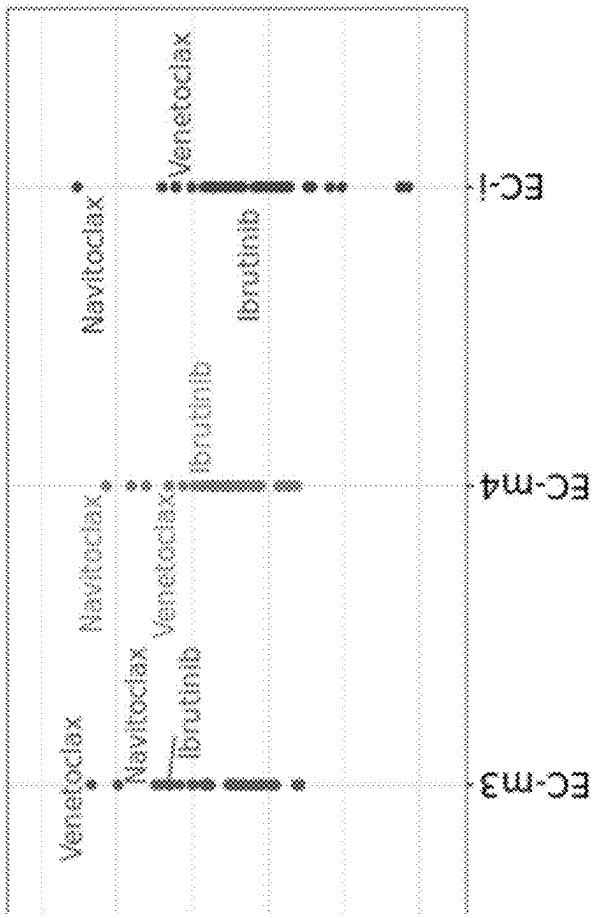


FIG. 12A (Continued)

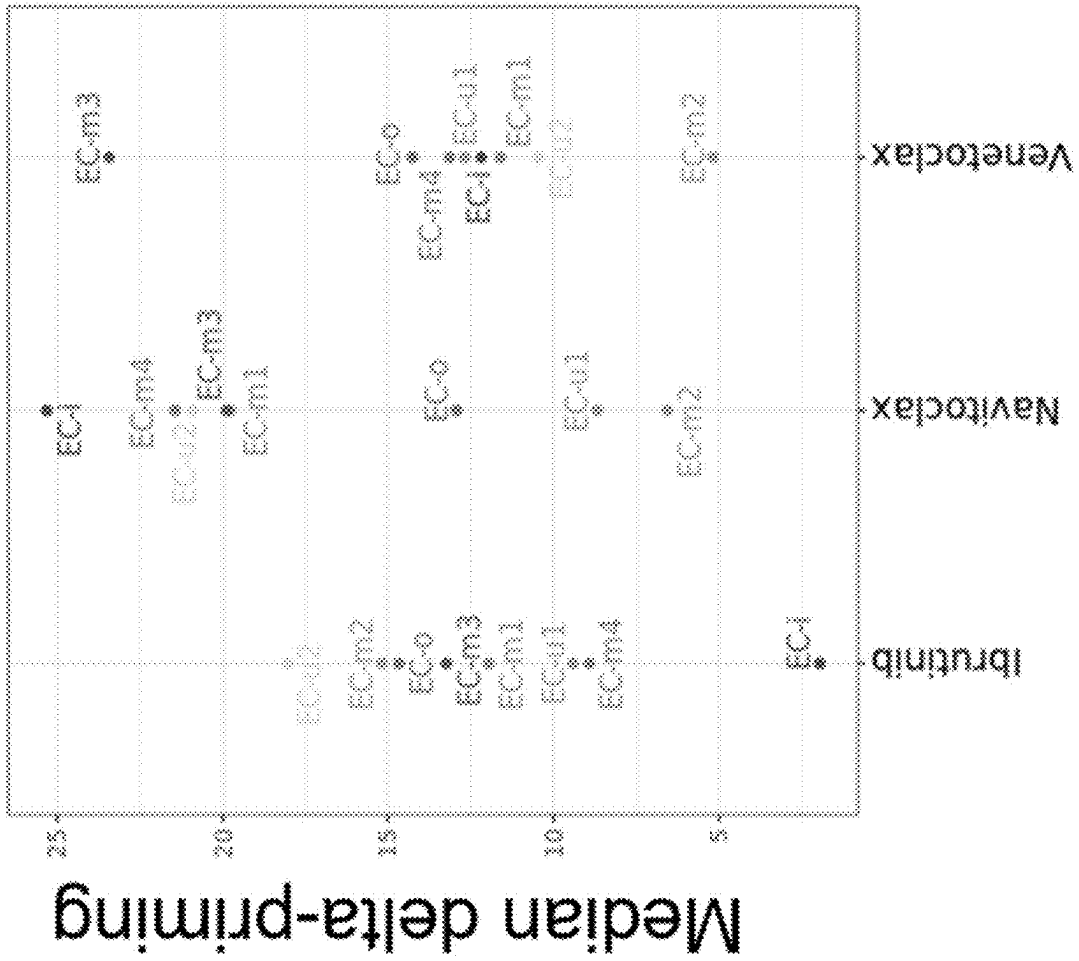

Median delta-priming
25
20
15
10
5
ibrutinib
Navitoclax
Venetoclax
EC-j
EC-m4
EC-u2
EC-m3
EC-m1
EC-m2
EC-o
EC-m3
EC-m1
EC-u1
EC-m4
EC-j
EC-o
EC-m4
EC-j
EC-u1
EC-m1
EC-u2
EC-m2
EC-m3

FIG. 12B

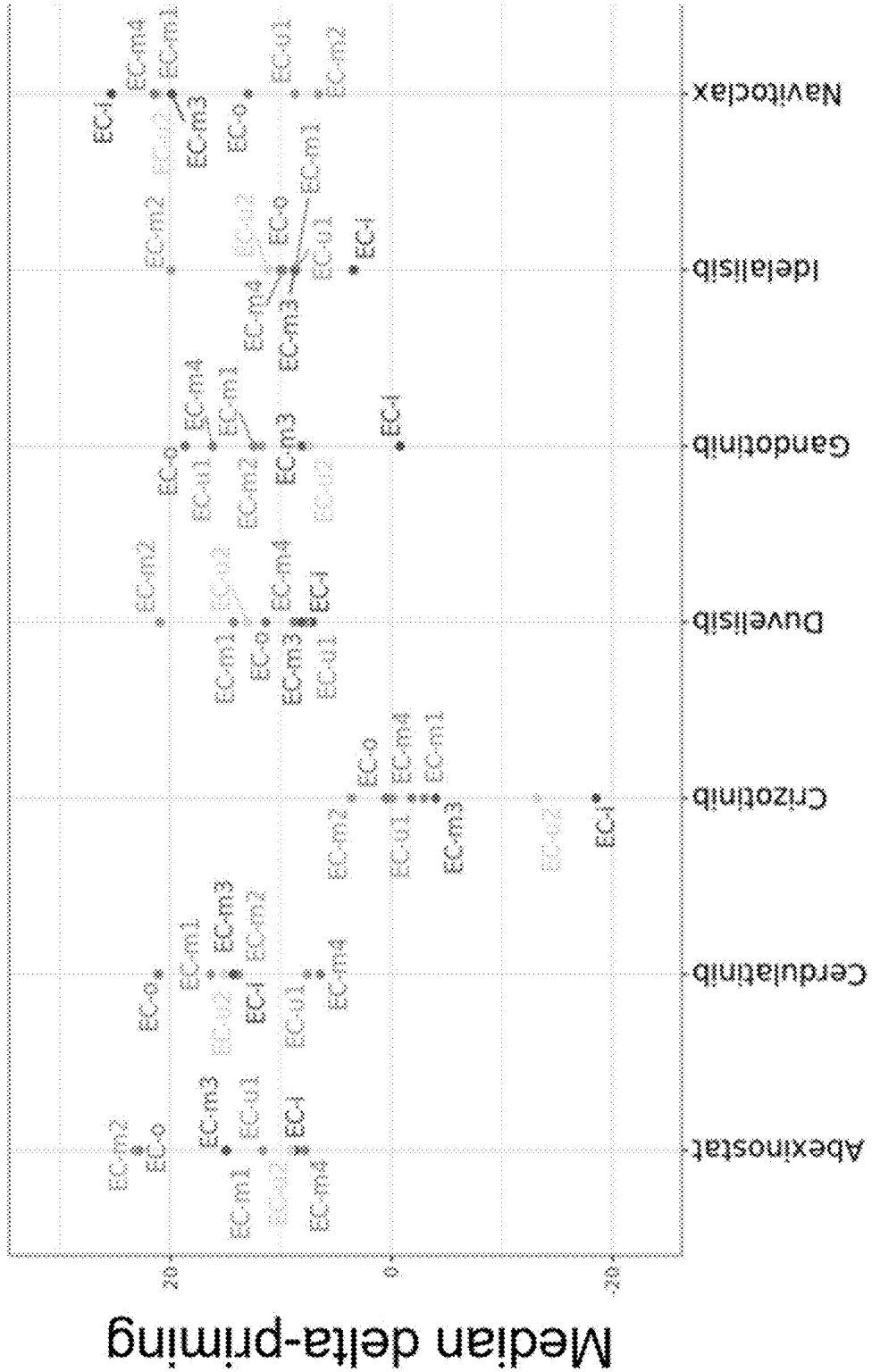

Median delta-priming
20
0
-20
Abexinostat
Cerdulatinib
Crizotinib
Duvelisib
Gandotinib
Idelalisib
Navitoclax

FIG. 12C

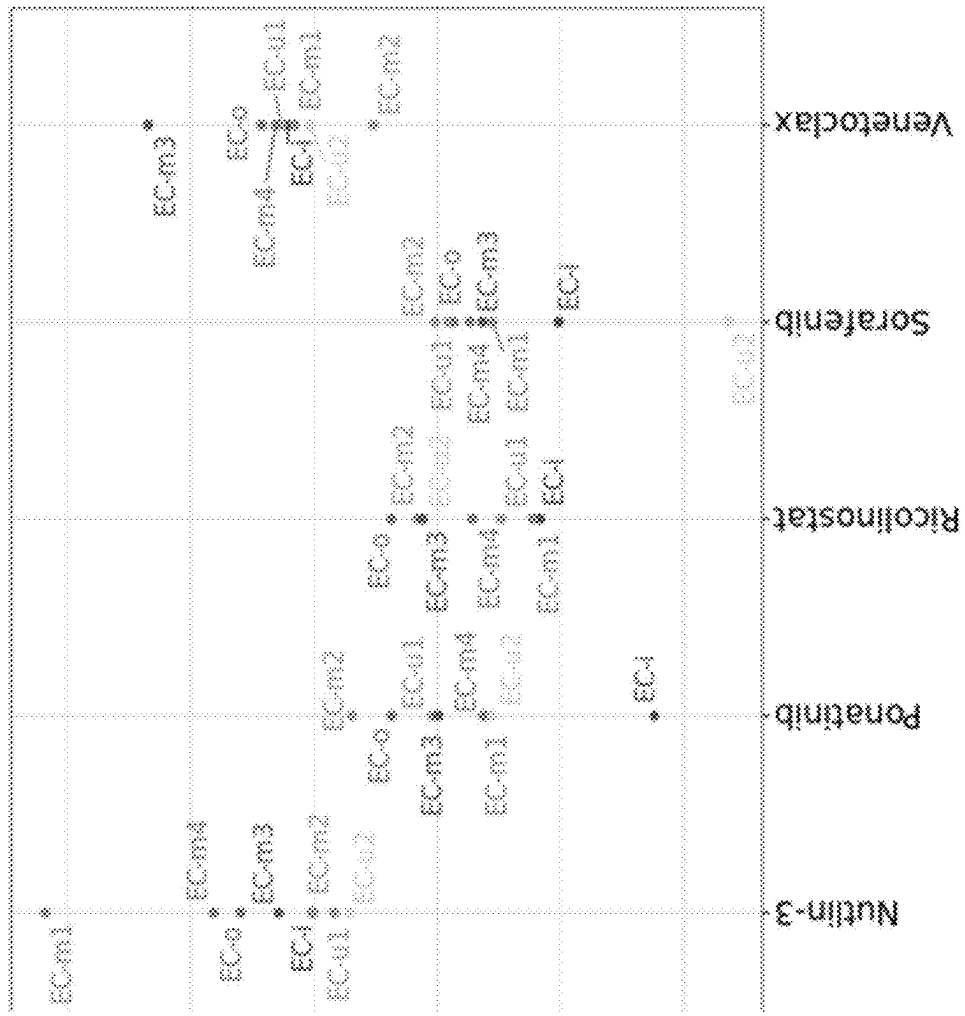


FIG. 12C (Continued)

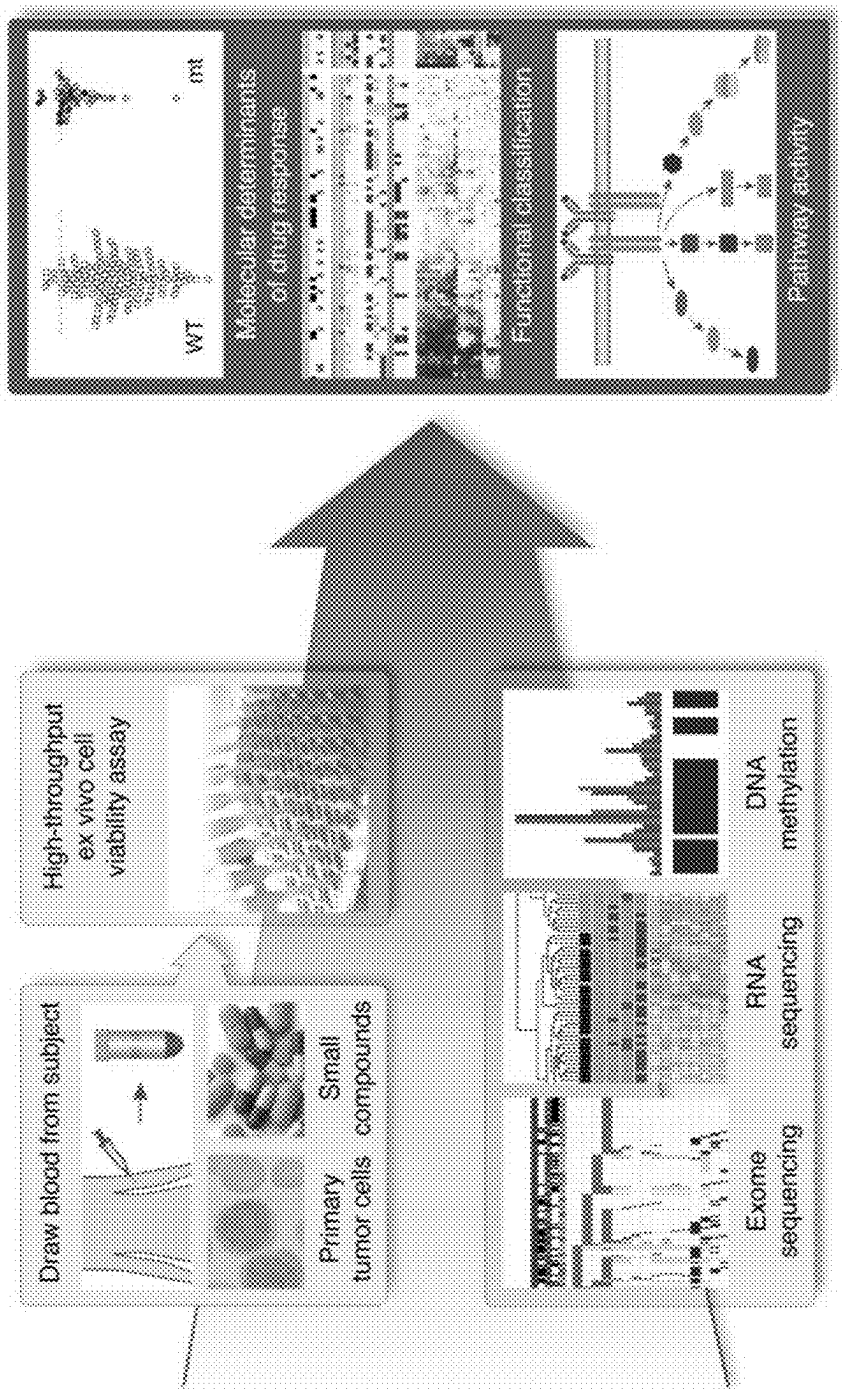

Draw blood from subject
Primary tumor cells
Small compounds
High-throughput ex vivo cell viability assay
Exome sequencing
RNA sequencing
DNA methylation
WT
mt
Molecular determinants of drug response
Functional classification
Pathway activity

FIG. 13

drug_name	M-CLL	U-CLL	i-CLL	m-CLL	n-CLL	EC-i	EC-m1	EC-m2	EC-m3	EC-m4	EC-o	EC-u1	EC-u2
A-1331852	9.80	9.75	10.65	9.41	10.12	6.86	10.44	8.25	9.58	11.30	10.42	8.82	17.19
AZD5991	3.38	4.22	3.19	3.24	3.87	7.42	1.49	7.56	4.86	3.01	2.94	4.21	7.06
AZD8055	4.29	1.88	4.09	4.29	3.16	-1.11	2.01	3.42	1.23	3.32	5.78	3.10	2.39
Abexinostat	15.40	10.43	8.42	16.91	10.64	8.61	14.80	23.74	16.64	8.11	21.49	10.97	9.08
Acalabrutinib	8.60	7.23	10.48	7.99	8.47	5.72	3.25	13.62	4.53	5.95	10.36	7.78	11.11
Atorvastatin	6.09	7.18	8.43	5.40	4.31	5.63	1.10	8.15	5.03	5.10	8.06	7.45	6.38
Azacitidine	2.20	2.08	1.79	2.54	2.23	0.47	1.48	5.56	2.76	1.78	2.90	-0.84	3.51
Bendamustine	2.30	3.38	3.73	1.92	2.78	4.44	2.57	5.55	4.22	1.15	2.07	2.72	5.70
Carfilzomib	6.84	3.80	10.26	4.61	5.12	5.22	7.47	11.79	3.49	5.90	6.26	3.75	9.52
Cerdulatinib	11.80	6.36	18.61	11.13	11.89	14.07	16.30	8.70	14.22	6.38	18.94	7.58	12.53
Crizotinib	-0.85	-4.08	-2.33	-0.92	0.50	-18.52	-2.94	5.05	-4.03	-1.80	0.33	0.63	-0.13
Dasatinib	9.55	6.87	11.39	8.92	8.21	4.05	9.97	10.10	12.44	6.95	9.74	7.93	9.61
Duvelisib	11.31	9.44	12.99	10.58	7.81	7.12	13.19	23.32	10.32	8.57	11.16	6.81	9.29
Entospletinib	7.79	6.35	7.29	7.79	7.26	1.73	3.01	15.43	8.16	5.86	13.99	5.32	10.72
Erastin	2.14	1.82	2.94	1.96	1.87	-1.72	0.31	2.48	0.74	2.39	2.48	2.12	5.24
Fludarabine	7.63	3.88	10.79	6.92	2.38	7.10	9.67	6.85	10.87	7.87	7.01	2.47	9.29
GSK690693	4.41	2.62	8.70	3.48	1.02	1.48	2.14	9.05	-4.28	3.71	10.51	1.35	6.96
Gandotinib	14.65	10.76	14.27	14.81	10.78	-0.78	12.42	11.93	8.70	15.92	24.71	16.02	9.37
Ibrutinib	10.88	9.63	10.96	10.81	10.52	1.96	12.23	14.68	11.69	8.92	14.30	8.73	19.74
Idelalisib	10.34	7.88	17.68	8.90	7.72	3.41	8.67	20.54	8.71	10.27	8.91	8.66	6.73
JQ1	0.84	0.73	3.35	0.52	0.74	-1.09	-0.59	5.56	-1.95	1.20	0.69	-0.50	3.32
Lenalidomide	1.91	0.37	2.23	1.98	0.37	1.04	0.36	11.36	3.37	-1.29	3.39	-1.66	3.72
MK-2206	6.56	5.65	5.62	7.03	4.19	-1.62	4.26	5.59	3.28	6.31	9.03	5.70	6.19
Navitoclax	15.86	10.01	16.93	15.15	8.78	25.32	19.79	5.99	18.82	20.94	11.94	6.57	14.32
Nirogacestat	7.54	4.48	7.21	7.76	4.65	7.21	6.16	11.85	7.72	6.95	6.70	2.32	8.17
Nutlin-3	14.93	9.29	19.90	13.44	9.23	10.15	30.39	10.09	12.89	16.67	12.60	8.20	5.59
Onalespib	4.68	7.61	1.89	5.27	13.14	5.85	2.43	10.21	7.90	1.53	6.98	10.09	8.48
Osimertinib	0.56	-0.06	-0.18	0.67	0.35	-5.26	-0.08	-0.37	-0.57	-1.50	4.12	-0.03	2.05
Ponatinib	0.52	-4.35	-7.43	1.05	2.73	-17.37	-3.87	7.72	-0.05	-3.85	2.64	0.45	3.07
Rapamycin	7.26	1.80	12.79	5.56	3.13	12.31	3.50	6.19	1.04	8.43	5.95	2.13	15.39
Ricolinostat	-0.71	-4.55	-6.29	0.74	-4.13	-10.41	-7.69	1.66	1.63	-3.22	2.55	-5.11	3.66
Ruxolitinib	3.23	-0.64	3.82	2.95	-0.64	-0.32	5.13	3.87	0.04	3.95	3.66	-0.65	4.21
Selinexor	6.20	4.04	6.06	6.06	3.28	8.17	10.09	3.98	5.31	5.43	6.64	5.07	10.07
Sorafenib	-2.31	-4.64	-4.98	-2.33	-3.52	-9.80	-4.12	-0.12	-4.19	-2.53	-1.78	-0.85	-3.94
Sunitinib	4.83	2.91	8.72	3.89	5.19	-5.83	0.21	5.96	2.31	4.83	7.91	3.49	4.76
Trametinib	5.44	5.57	8.00	4.86	3.94	1.32	0.79	6.49	2.45	3.69	6.96	5.68	14.24
Umbralisib	6.21	3.79	9.98	4.77	4.32	-2.27	0.00	10.51	5.02	6.45	6.25	4.53	4.24
Vecabrutinib	7.23	6.12	7.46	7.18	6.45	6.11	6.86	4.85	9.31	6.87	7.18	6.62	9.71
Venetoclax	12.93	9.76	11.49	12.92	9.64	12.18	10.67	5.19	23.44	13.14	13.55	13.48	13.37
Vorinostat	5.07	3.63	1.89	5.97	3.96	-2.69	-5.75	15.30	10.79	2.12	13.91	1.68	5.43
Voruciclib	4.24	4.99	7.29	3.90	2.80	5.38	-1.61	3.61	0.52	4.58	7.00	4.96	4.52
Zanubrutinib	6.87	7.82	8.87	6.78	7.09	7.50	1.28	10.59	4.69	5.14	9.03	6.93	10.05

FIG. 14

driver_ATM	driver_CARD11	driver_CHD2	driver_FBXW7	driver_ITIH2	driver_MYD88	driver_NOTCH1	driver_NRAS
5.70	2.76	6.27	9.35	15.17	4.46	18.03	9.35
2.96	5.99	1.14	5.63	5.90	1.77	3.94	2.91
8.15		11.56	8.15	8.97	4.65	-3.88	15.58
6.37	16.32	18.96	29.31	11.67	17.68	-1.91	6.78
9.32	8.22	9.35	7.32	15.41	12.51	4.36	5.08
8.66		6.64	5.45	9.43	10.67	8.18	4.04
0.38	29.63	0.65	2.75	14.81	6.44	2.08	2.88
3.90	2.44	3.56	2.65	-0.61	1.35	1.11	8.93
3.05	12.75	9.80	8.04	10.05	5.66	1.88	6.80
25.08	-1.41	7.76	18.68	9.58	7.20	-14.70	22.50
-4.06	0.73	2.31	4.77	8.89	-4.12	-37.12	-4.66
15.89	7.34	16.58	10.10	10.14	14.95	-16.01	8.19
5.76	3.79	13.65	11.91	22.23	7.23	1.17	15.76
8.61	19.91	12.59	7.62	10.78	10.53	-2.23	10.57
2.03	0.98	2.92	1.22	6.62	0.43	3.76	3.71
0.71	6.78	6.27	3.88	25.39	7.13	10.92	2.74
0.23	-6.46	5.72	3.71	9.92	-0.55	5.79	1.94
15.16	9.81	16.14	13.84	14.46	3.16	8.11	19.29
5.77	5.28	14.16	13.29	17.78	0.25	13.29	18.78
10.41	7.57	12.96	13.98	22.26	15.22	-1.34	9.87
-0.12	3.20	3.83	4.76	5.31	-1.09	-1.81	0.80
-2.15	3.29	8.03	7.95	17.26	-1.69	-0.98	1.40
6.57	-2.75	10.62	3.44	12.54	1.09	1.36	9.01
21.39	3.70	7.55	5.79	5.87	20.69	6.29	13.52
3.45	5.75	11.30	8.12	15.23	8.06	3.28	7.47
5.90	3.77	1.51	3.54	5.10	11.01	6.01	5.01
16.74	18.64	8.97	7.64	-2.02	1.41	-4.88	30.68
0.01		3.46	-2.08	10.70	-12.26	-2.79	6.60
7.40	-7.05	0.33	2.03	1.35	-12.75	-41.83	8.73
5.30	1.38	10.26	4.89	9.70	9.71	33.69	4.66
-3.32	35.92	-0.92	-1.29	-1.17	-1.62	-9.04	-3.62
1.37		0.85	-0.75	-2.13	3.90	-1.56	-0.63
7.11	6.05	4.85	3.32	21.07	16.56	3.91	2.01
-0.39		0.67	4.29	1.94	-4.90	-15.87	-1.68
4.59		2.04	0.68	-1.06	-0.70	-11.85	14.59
5.05		16.04	12.46	32.60	0.27	2.98	11.44
5.90	5.27	8.95	7.86	20.05	7.51	-4.01	5.05
8.32	4.68	8.72	4.91	4.32	2.75	-0.73	10.49
12.43	-5.96	7.75	9.45	11.61	8.34	4.41	7.68
-1.81	7.69	7.95	12.82	0.83	3.33	-10.54	1.66
5.12		6.74	5.92	0.48	2.51	2.65	10.36
9.53	1.76	11.42	0.89	-0.35	0.57	14.05	17.42

FIG. 14 (Continued)

driver_POT1	driver_SF3B1	driver_TP53	driver_ZMYM3	driver_gain_7q22.1	driver_gain_15q24.2	driver_gain_16p11.2
12.73	3.10	6.95	8.99	15.12	10.34	7.02
9.19	2.68	2.83	5.67	4.02	3.77	6.47
4.43	3.75	7.38	-0.60	4.19	7.77	5.64
4.43	7.87	26.81	24.85	33.47	29.65	8.42
10.61	6.58	10.93	0.50	8.36	15.45	7.55
14.25	11.98	10.94	-0.03	4.59	5.36	10.67
0.97	-0.02	-0.26	-5.44	2.67	9.38	3.16
3.58	2.93	1.05	1.31	4.38	2.27	2.57
4.83	6.64	18.73	-0.58	4.33	10.31	5.66
4.95	5.28	35.06	0.50	28.20	37.05	13.56
0.73	0.73	6.61	31.70	-0.84	-9.05	-1.74
8.54	5.78	20.02	0.08	8.64	12.72	10.30
2.22	5.36	21.40	6.01	11.30	13.80	14.82
1.27	6.72	25.75	4.74	6.26	5.19	6.19
3.69	0.64	1.11	0.50	1.38	7.35	2.30
-3.86	0.53	0.63	-1.32	6.75	4.12	5.14
-2.19	-1.25	7.77	-0.81	4.07	4.99	0.45
11.14	9.63	19.75	25.58	11.42	21.82	9.72
7.83	3.02	11.46	8.48	17.42	13.84	1.31
9.03	7.57	22.89	4.98	11.66	9.65	19.42
-3.11	-0.07	2.74	2.65	3.41	5.92	3.67
-3.07	-0.57	0.93	0.17	6.20	6.66	-0.16
3.52	4.98	3.43	0.93	4.65	10.71	3.04
10.86	10.30	4.78	12.98	13.11	14.09	38.31
0.81	5.80	9.53	0.33	6.28	8.77	8.06
4.52	6.40	1.71	3.54	11.06	26.71	4.78
14.60	11.30	4.44	8.49	6.89	5.14	-4.30
0.01	-1.73	-0.43	-0.47	2.29	-0.82	-6.27
0.45	0.01	13.00	9.49	3.51	-6.97	-8.05
1.01	3.26	10.58	-14.12	10.83	15.84	9.51
-5.70	-6.90	-4.69	-4.53	6.69	3.60	-5.81
-2.03	-1.08	0.23	-3.04	-0.47	4.26	0.43
6.29	4.24	3.32	3.63	7.23	1.10	18.24
3.67	-0.67	6.17	-3.68	-2.50	-8.31	-3.27
1.12	0.19	8.38	-0.44	9.25	4.22	-0.70
4.45	1.80	15.83	-0.62	5.37	4.35	2.14
7.05	5.27	13.92	-0.19	7.51	6.40	4.86
6.83	6.62	10.93	0.08	10.76	19.26	3.85
16.35	9.15	5.60	9.92	6.48	17.80	13.13
-3.97	-4.75	7.73	7.44	16.78	5.92	-0.14
4.06	2.07	8.33	5.86	3.26	4.93	1.32
6.23	5.89	20.44	-11.70	8.96	13.74	0.07

FIG. 14 (Continued)

driver_gain_19p13.3	driver_loss_1q21.3	driver_loss_1q42.13	driver_loss_2p11.2	driver_loss_2q31.1	driver_loss_3p21.31
9.10	5.95	8.44	4.32	6.03	7.02
3.16	2.42	16.87	0.18	1.96	1.64
5.06	7.18		6.96	4.61	4.84
16.09	9.72	14.13	4.43	13.44	10.51
6.04	7.56	11.30	9.13	6.88	8.36
5.36	4.04	2.10	8.00	2.59	5.12
1.53	1.54		0.99	1.09	2.12
2.97	2.91	12.07	5.11	3.98	2.91
6.78	2.55	12.75	3.03	6.08	4.33
8.65	8.64	17.15	2.28	6.83	22.22
-0.83	-1.11	0.73	-3.05	-0.99	-2.34
6.78	8.51	13.37	10.55	6.19	10.34
11.31	11.87	3.64	10.43	8.99	11.30
5.12	5.98	24.74	1.93	5.06	6.40
1.57	2.68	6.97	1.17	0.57	0.68
3.79	6.75		-1.95	3.88	4.75
2.90	2.24	-6.46	-1.10	0.84	1.48
14.27	17.38	9.81	13.31	19.81	10.46
10.36	4.96	6.23	4.67	3.52	1.92
9.37	12.96	7.57	10.40	9.96	13.26
3.48	-0.15	3.20	0.40	-0.27	2.80
2.73	0.26	-2.23	-0.27	-1.37	-0.59
3.35	7.38	-2.75	9.12	2.99	2.48
11.11	18.36	10.18	20.41	14.82	28.81
7.27	10.86	9.60	3.45	9.71	6.28
10.36	10.97	3.77	11.21	6.49	11.06
6.04	2.21	23.75	13.37	10.43	2.47
0.28	-1.55	4.30	0.42	-0.67	-5.02
-2.46	-5.13	-7.05	9.16	-7.45	-7.55
9.77	9.31	1.38	2.56	8.87	9.71
-4.67	-3.02		-6.90	-4.75	-1.58
0.02	0.83		-2.93	0.85	1.04
2.08	9.71	12.55	0.82	5.58	9.19
-2.48	-3.89		3.40	-4.87	-4.16
2.91	-0.58		11.46	-0.56	5.75
6.17	10.54		7.51	1.28	3.11
5.08	7.43	5.27	5.81	6.46	5.87
4.63	4.51	10.41	7.47	3.69	7.16
8.57	9.90	9.83	6.04	9.86	9.23
4.46	0.83	8.03	-3.16	2.18	1.19
3.50	3.42		5.27	5.10	3.10
5.50	8.49	1.76	13.72	2.71	7.34

FIG. 14 (Continued)

driver_loss_3p13	driver_loss_5p15.33	driver_loss_7p22.2	driver_loss_9q34.3	driver_loss_10p12.2	driver_loss_10q24.2
11.21	6.03	7.32	7.27	6.03	9.13
13.95	2.37	3.62	4.41	1.96	2.85
-10.79	6.00	6.73	1.07	4.61	2.98
24.60	9.68	9.68	6.87	13.44	20.07
10.25	7.93	7.62	6.58	6.88	8.20
5.65	2.59	2.60	4.84	2.59	3.10
1.95	1.31	2.21	1.48	1.09	0.91
3.72	4.64	5.06	2.93	3.98	3.38
12.75	6.08	5.66	7.47	6.08	5.25
-3.44	6.44	7.17	12.07	6.83	4.39
-2.80	-3.06	-1.11	-0.73	-0.99	-0.84
-7.56	7.45	8.57	7.34	6.19	4.01
12.46	8.99	11.52	3.74	8.99	12.21
19.80	4.78	4.78	16.74	5.06	4.11
4.46	2.17	2.94	4.46	0.57	2.17
-0.75	5.87	6.75	-0.38	3.88	3.37
-4.55	0.97	2.24	-0.40	0.84	1.08
11.92	17.38	17.38	7.35	19.81	20.28
9.60	2.93	4.59	8.76	3.52	6.67
11.99	10.41	10.37	7.68	9.96	11.99
6.60	-2.71	-0.15	1.16	-0.27	1.28
-3.40	-1.66	0.35	-1.85	-1.37	-2.15
0.52	4.23	7.38	0.89	2.99	5.58
3.81	25.25	18.14	15.57	14.82	10.69
1.11	10.77	11.23	4.43	9.71	9.71
3.77	6.49	5.73	4.96	6.49	6.49
10.62	8.10	6.94	12.42	10.43	5.87
0.01	0.12	0.80	-0.93	-0.67	0.33
-11.19	-7.66	-5.13	-6.71	-7.45	-7.34
0.45	9.33	9.31	2.80	8.87	0.97
-2.58	-6.67	-3.57	-10.63	-4.75	-4.75
3.09	2.10	0.78	1.51	0.85	0.75
11.47	7.09	8.18	7.56	5.58	3.22
2.23	-4.94	-3.89	-4.44	-4.87	-0.56
11.66	-0.56	-0.58	0.09	-0.56	3.57
0.63	8.20	10.54	-0.41	1.28	3.08
4.79	8.61	7.43	2.37	6.46	5.30
9.00	4.81	4.07	7.87	3.69	3.01
5.47	9.08	9.19	10.22	9.86	9.19
1.29	1.19	2.15	-5.81	2.18	6.85
4.26	5.10	3.42	-2.05	5.10	9.73
10.33	8.71	8.49	1.32	2.71	10.33

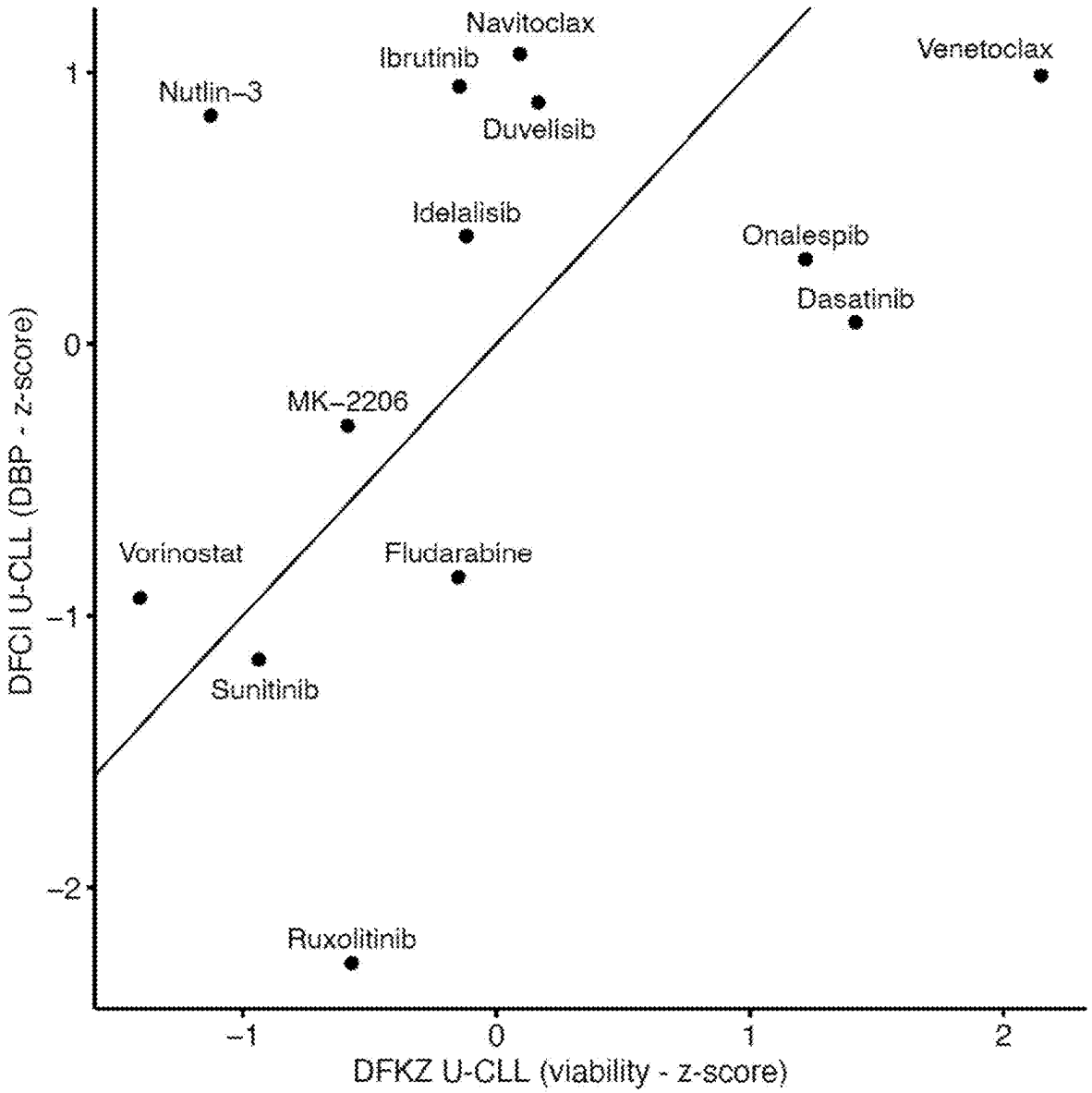
FIG. 14 (Continued)

driver_loss_10q24.32	driver_loss_11q22.3	driver_loss_12p13.31a	driver_loss_13q14.13	driver_loss_13q14.3
10.81	3.58	6.03	8.24	9.28
2.58	2.63	2.37	2.94	3.41
-3.22	3.80	6.00	4.12	4.43
25.52	10.64	9.68	17.48	13.92
13.54	4.88	7.93	9.13	8.58
5.65	4.58	2.59	8.03	6.17
0.42	0.61	1.31	3.89	2.49
1.50	3.72	4.64	3.36	2.90
2.98	6.80	6.08	7.72	6.53
-1.49	21.43	6.44	25.34	17.43
-11.27	-0.07	-3.06	-1.12	-1.72
-6.35	5.91	7.45	11.77	9.22
18.72	9.12	8.99	9.27	10.79
2.21	8.85	4.78	10.81	7.99
3.25	0.59	2.17	2.54	2.30
-5.30	2.39	5.87	10.95	7.17
-0.04	-0.77	0.97	9.18	4.16
11.93	14.15	17.38	15.98	14.30
6.40	5.38	2.93	9.31	10.76
21.84	7.57	10.41	12.35	10.44
19.38	0.84	-2.71	0.88	0.69
-18.93	1.40	-1.66	1.58	0.69
6.66	5.24	4.23	8.23	6.22
10.90	11.05	25.25	19.66	15.80
3.31	5.80	10.77	7.46	6.45
11.37	8.09	6.49	13.07	11.71
-10.40	14.56	8.10	6.89	5.74
-7.07	-0.42	0.12	1.24	0.04
-25.19	0.45	-7.66	-5.63	-0.77
-8.65	3.65	9.33	4.89	5.69
-21.19	-4.38	-6.67	0.91	-1.61
0.82	-1.07	2.10	6.36	3.00
3.28	5.12	7.09	9.00	5.47
2.23	-3.47	-4.94	-4.46	-2.13
11.66	2.56	-0.56	5.16	4.83
0.63	1.80	8.20	6.12	5.45
4.29	3.83	8.61	7.58	5.55
1.93	6.62	4.81	9.01	7.95
4.20	10.09	9.08	14.47	13.42
6.10	0.50	1.19	13.35	4.35
4.26	3.50	5.10	4.77	4.06
11.08	4.35	8.71	7.45	7.66

FIG. 14 (Continued)

driver_loss_14q32.12	driver_loss_16q22.1	driver_loss_17p13.3	driver_loss_17p13.1	driver_tri_12	driver_gain_2p
7.60	7.32	6.03	6.96	11.19	4.32
2.94	2.55	2.37	10.30	5.69	0.18
4.56	6.00	6.00	20.98	8.04	6.96
8.20	13.44	9.68	32.67	13.75	4.43
8.20	8.31	8.31	15.23	16.05	9.13
3.32	3.50	2.59	9.43	13.27	8.00
2.58	1.31	1.31	2.30	3.96	0.99
4.72	3.74	4.72	5.83	5.40	5.11
8.80	7.18	4.32	20.40	9.94	3.03
6.47	6.44	6.44	31.35	9.94	2.28
-4.12	-3.40	-4.12	8.89	5.26	-3.05
10.56	4.92	7.45	26.63	10.12	10.55
11.17	9.92	8.99	36.61	20.31	10.43
3.63	3.05	4.78	28.38	11.40	1.93
0.21	2.17	2.17	1.42	3.36	1.17
-0.03	2.88	5.87	1.90	9.17	-1.95
-0.55	0.05	0.97	5.97	8.70	-1.10
3.16	16.90	17.38	12.36	11.55	13.31
1.25	3.40	2.93	16.50	16.79	4.67
12.19	7.49	9.84	32.46	11.54	10.40
-1.09	-0.15	-2.71	5.69	3.87	0.40
-4.37	-0.03	-1.76	11.65	9.41	-0.27
1.09	8.35	6.25	-0.73	5.84	9.12
34.75	17.25	25.25	4.43	7.58	20.41
9.68	9.90	10.77	11.85	11.89	3.45
2.62	13.24	12.11	-0.74	4.92	11.21
7.20	6.82	8.10	17.16	4.94	13.37
-1.55	0.32	0.12	-3.83	2.97	0.42
-12.75	-5.26	-7.66	1.35	8.73	9.16
9.71	10.41	8.94	9.70	14.72	2.56
-8.13	-6.67	-6.67	-5.23	-1.04	-6.90
1.21	0.85	2.10	-1.74	1.03	-2.93
8.26	5.27	7.09	2.71	7.98	0.82
-4.90	-4.63	-4.94	1.94	1.18	3.40
-0.70	0.52	-0.56	-1.06	4.57	11.46
0.27	6.17	8.20	18.73	14.65	7.51
7.51	3.86	6.64	10.51	9.85	5.81
4.10	4.16	4.16	8.95	4.89	7.47
9.08	9.08	9.08	5.68	5.19	6.04
-2.46	1.19	1.19	12.70	6.09	-3.16
2.51	3.50	5.10	3.43	4.52	5.27
0.57	7.37	8.71	-0.35	14.07	13.72

FIG. 14 (Continued)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Ibrutinib
Venetoclax
Nutlin–3
Duvelisib
Idelalisib
Onalespib
Dasatinib
MK–2206
Vorinostat
Fludarabine
Sunitinib
Ruxolitinib
1
0
–1
–2
–1
0
1
2
DFCI U-CLL (DBP - z-score)
DFKZ U-CLL (viability - z-score)

FIG. 15

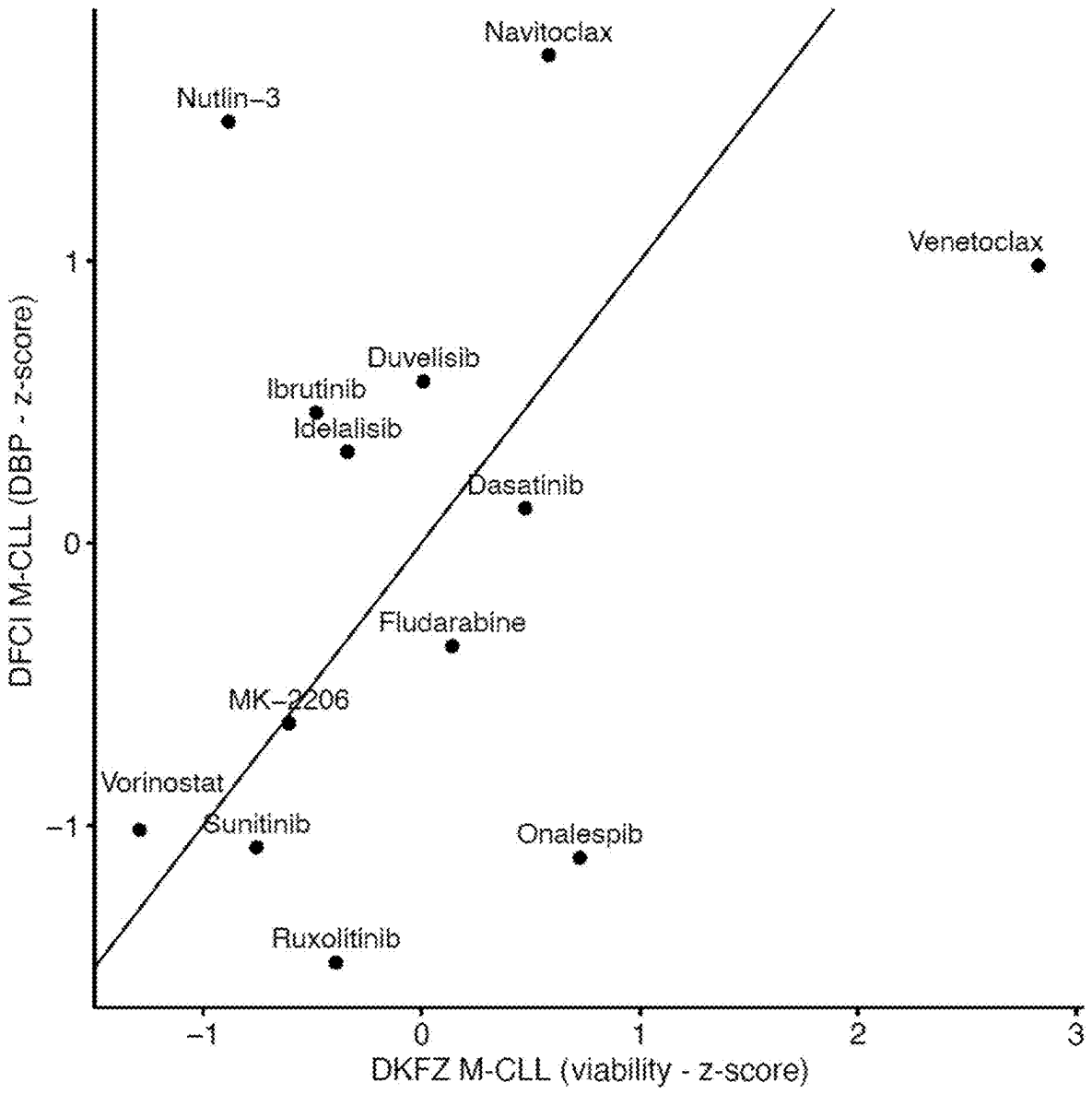

Navitoclax
Nutlin−3
Venetoclax
Duvelisib
Ibrutinib
Idelalisib
Dasatinib
Fludarabine
MK−2206
Vorinostat
Sunitinib
Onalespib
Ruxolitinib
1
0
−1
−1
0
1
2
3
DFCI M-CLL (DBP - z-score)
DKFZ M-CLL (viability - z-score)

FIG. 16

Median delta-priming across healthy donors per normal cell type			
drug_name	CD14	CD19	CD3
A-1331852	-4.668	-1.642	-5.991
AZD5991	-4.455	0.719	2.168
AZD8055	-6.212	7.914	-1.944
Abexinostat	-3.357	5.761	9.915
Acalabrutinib	4.454	1.996	2.749
Azacitidine	-10.79	1.973	-11.733
Bendamustine	-0.157	-0.455	-4.134
Carfilzomib	-19.873	-2.145	-18.46
Cerdulatinib	0.727	-3.872	-21.038
Dasatinib	-9.172	-1.647	-7.942
Duvelisib	-7.179	-4.193	-0.238
Entospletinib	-13.691	4.173	-6.27
Erastin	1.663	-0.767	1.194
Fludarabine	-5.989	-1.943	-10.125
GSK690693	-2.795	4.274	-6.262
Gandotinib	7.718	0.425	0.863
Ibrutinib	-4.095	-0.05	-8.293
Idelalisib	3.477	2.212	-6.717
JQ1	-17.015	9.74	-8.499
Lenalidomide	-10.196	3.425	-9.572
MK-2206	-5.463	5.242	-8.978
Navitoclax	-1.02	0.85	-3.213
Nirogacestat	-7.709	-1.045	-7.775
Nutlin-3	-14.504	-6.812	-21.098
Onalespib	-3.388	3.832	-7.44
Osimertinib	-16.947	5.976	-17.675
Ricolinostat	1.666	5.601	-5.769
Ruxolitinib	-8.991	1.456	-15.624
Selinexor	-7.999	-0.383	-6.653
Trametinib	4.613	8.05	-4.332
Umbralisib	5.35	0.601	-0.743
Vecabrutinib	-1.226	6.661	-0.267
Venetoclax	-2.572	49.388	6.478
Vorinostat	-4.617	5.386	-0.079
Voruciclib	-6.376	8.895	-8.74

FIG. 17

drug_name*	Normals**	M-CLL	U-CLL	I-CLL	m-CLL
A-1331852	-3.388	13.187	13.133	14.035	12.799
AZD5991	0.331	3.048	3.886	2.859	2.913
AZD8055	-1.944	6.236	3.819	6.03	6.236
Abexinostat	5.344	10.059	5.088	3.071	11.564
Acalabrutinib	2.659	5.941	4.566	7.823	5.329
Azacitidine	-5.428	7.631	7.507	7.218	7.964
Bendamustine	-2.488	4.792	5.865	6.214	4.408
Carfilzomib	-13.043	19.881	16.842	23.301	17.649
Cerdulatinib	-7.181	18.983	13.537	25.793	18.307
Dasatinib	-4.687	14.235	11.556	16.074	13.608
Duvelisib	-2.152	13.467	11.592	15.146	12.735
Entospletinib	-6.166	13.952	12.511	13.457	13.952
Erastin	0.483	1.66	1.34	2.459	1.476
Fludarabine	-7.523	15.151	11.4	18.318	14.445
GSK690693	-0.995	5.405	3.614	9.694	4.472
Gandotinib	1.726	12.922	9.03	12.548	13.083
Ibrutinib	-3.825	14.708	13.451	14.783	14.638
Idelalisib	0.86	9.479	7.021	16.824	8.04
JQ1	-3.979	4.821	4.713	7.326	4.501
Lenalidomide	-6.764	8.673	7.138	8.992	8.741
MK-2206	-2.557	9.115	8.21	8.177	9.59
Navitoclax	-1.275	17.131	11.286	18.206	16.428
Nirogacestat	-6.615	14.151	11.099	13.827	14.377
Nutlin-3	-12.009	26.942	21.295	31.912	25.447
Onalespib	-3.297	7.977	10.905	5.183	8.563
Osimertinib	-6.999	7.557	6.936	6.816	7.672
Ricolinostat	1.512	-2.224	-6.061	-7.801	-0.776
Ruxolitinib	-7.816	11.048	7.175	11.636	10.763
Selinexor	-4.851	11.048	8.891	10.91	10.912
Trametinib	1.995	3.447	3.572	6.005	2.863
Umbralisib	2.326	3.888	1.46	7.651	2.442
Vecabrutinib	0.152	7.077	5.973	7.309	7.025
Venetoclax	5.281	7.653	4.475	6.213	7.637
Vorinostat	0.517	4.553	3.113	1.369	5.45
Voruciclib	-2.261	6.499	7.253	9.55	6.166

FIG. 18

n-CLL	EC-i	EC-m1	EC-m2	EC-m3	EC-m4
13.511	10.248	13.826	11.641	12.971	14.689
3.541	7.089	1.162	7.228	4.526	2.678
5.104	0.835	3.949	5.359	3.173	5.26
5.296	3.271	9.455	18.393	11.298	2.767
5.807	3.065	0.589	10.962	1.874	3.29
7.656	5.896	6.907	10.985	8.187	7.208
5.271	6.932	5.058	8.041	6.704	3.639
18.163	18.266	20.517	24.831	16.528	18.947
19.069	21.254	23.486	15.878	21.4	13.556
12.892	8.736	14.662	14.79	17.126	11.635
9.963	9.271	15.342	25.47	12.47	10.723
13.429	7.893	9.173	21.601	14.33	12.025
1.384	-2.205	-0.171	1.997	0.26	1.905
9.899	14.62	17.196	14.375	18.395	15.393
2.018	2.472	3.13	10.048	-3.282	4.708
9.049	-2.507	10.691	10.201	6.972	14.195
14.348	5.786	16.059	18.509	15.515	12.742
6.86	2.551	7.806	19.679	7.846	9.407
4.72	2.889	3.392	9.536	2.024	5.175
7.138	7.803	7.127	18.127	10.134	5.474
6.744	0.937	6.82	8.142	5.841	8.865
10.056	26.591	21.066	7.265	20.094	22.219
11.261	13.824	12.775	18.469	14.339	13.561
21.243	22.163	42.395	22.096	24.902	28.681
16.436	9.144	5.728	13.511	11.2	4.83
7.347	1.737	6.922	6.627	6.426	5.494
-5.647	-11.923	-9.2	0.143	0.122	-4.733
7.175	7.498	12.944	11.685	7.859	11.764
8.129	13.017	14.945	8.831	10.16	10.281
1.941	-0.68	-1.201	4.5	0.457	1.696
1.995	-4.596	-2.325	8.188	2.692	4.12
6.293	5.958	6.712	4.698	9.157	6.723
4.356	6.903	5.391	-0.092	18.157	7.855
3.447	-3.211	-6.264	14.778	10.275	1.599
5.064	7.636	0.654	5.874	2.777	6.841

FIG. 18 (Continued)

EC-o	EC-u1	EC-u2	driver_ATM	driver_CARD11	driver_CHD2
13.812	12.207	20.579	9.089	6.144	9.656
2.605	3.875	6.726	2.626	5.663	0.814
7.723	5.045	4.331	10.091		13.505
16.147	5.629	3.738	1.028	10.976	13.617
7.697	5.125	8.452	6.666	5.558	6.69
8.325	4.588	8.94	5.812	35.061	6.082
4.556	5.205	8.187	6.385	4.925	6.05
19.306	16.791	22.562	16.09	25.789	22.847
26.123	14.757	19.707	32.262	5.775	14.94
14.425	12.62	14.294	20.579	12.025	21.264
13.311	8.961	11.445	7.917	5.937	15.804
20.154	11.487	16.886	14.772	26.076	18.756
1.999	1.641	4.753	1.55	0.497	2.44
14.534	9.993	16.813	8.229	14.306	13.794
11.501	2.347	7.954	1.223	-5.462	6.711
22.979	14.294	7.64	13.433	8.085	14.415
18.126	12.558	23.56	9.594	9.109	17.983
8.045	7.795	5.87	9.549	6.712	12.104
4.667	3.48	7.301	3.858	7.175	7.811
10.158	5.101	10.48	4.612	10.053	14.79
11.584	8.258	8.749	9.123	-0.191	13.178
13.22	7.841	15.597	22.666	4.977	8.82
13.316	8.934	14.78	10.06	12.367	17.919
24.613	20.209	17.604	17.908	15.775	13.516
10.272	13.387	11.78	20.04	21.936	12.266
11.12	6.973	9.048	7.013		10.458
1.035	-6.627	2.149	-4.831	34.41	-2.437
11.474	7.164	12.022	9.19		8.668
11.491	9.916	14.923	11.965	10.905	9.704
4.961	3.687	12.244	3.052		14.041
3.926	2.204	1.91	3.573	2.945	6.62
7.029	6.473	9.553	8.167	4.533	8.568
8.264	8.199	8.09	7.15	-11.245	2.467
13.389	1.165	4.908	-2.327	7.169	7.437
9.256	7.223	6.78	7.376		9.001

FIG. 18 (Continued)

driver_FBXW7	driver_ITIH2	driver_MYD88	driver_NOTCH1	driver_NRAS	driver_POT1
12.737	18.557	7.848	21.422	12.741	16.12
5.298	5.565	1.443	3.609	2.577	8.855
10.099	10.912	6.597	-1.932	17.519	6.378
23.963	6.321	12.335	-7.253	1.433	-0.91
4.665	12.755	9.855	1.696	2.417	7.948
8.178	20.241	11.87	7.507	8.31	6.401
5.136	1.88	3.842	3.601	11.418	6.067
21.078	23.095	18.703	14.918	19.839	17.872
25.865	16.765	14.382	-7.521	29.685	12.135
14.79	14.828	19.64	-11.326	12.88	13.223
14.063	24.379	9.385	3.32	17.914	4.367
13.786	16.943	16.695	3.934	16.738	7.436
0.736	6.134	-0.057	3.274	3.228	3.207
11.4	33.114	14.65	18.445	10.264	3.662
4.708	10.918	0.449	6.786	2.933	-1.191
12.114	12.733	1.437	6.388	17.565	9.419
17.114	21.605	4.07	17.111	22.609	11.654
13.116	21.405	14.365	-2.204	9.011	8.165
8.737	9.286	2.889	2.17	4.778	0.873
14.716	24.023	5.074	5.788	8.168	3.692
5.993	15.102	3.652	3.913	11.568	6.079
7.069	7.149	21.966	7.564	14.792	12.135
14.739	21.841	14.679	9.899	14.085	7.424
15.549	17.106	23.024	18.015	17.022	16.528
10.932	1.276	4.706	-1.584	33.98	17.897
4.916	17.7	-5.264	4.209	13.601	7.007
-2.806	-2.68	-3.131	-10.551	-5.131	-7.212
7.068	5.691	11.716	6.259	7.187	5.788
8.172	25.921	21.412	8.761	6.862	11.14
10.467	30.603	-1.725	0.982	9.444	2.456
5.529	17.729	5.186	-6.334	2.726	4.72
4.756	4.173	2.594	-0.88	10.338	6.678
4.167	6.325	3.055	-0.873	2.398	11.071
12.305	0.316	2.816	-11.06	1.142	-4.485
8.176	2.743	4.767	4.913	12.623	6.318

FIG. 18 (Continued)

driver_SF3B1	driver_TP53	driver_ZMYM3	driver_gain_7q 22.1	driver_gain_15 q24.2	driver_gain_16 p11.2
6.492	10.335	12.376	18.504	13.724	10.404
2.351	2.501	5.341	3.686	3.438	6.139
5.691	9.323	1.346	6.133	9.711	7.58
2.525	21.469	19.506	28.129	24.306	3.071
3.923	8.268	-2.158	5.7	12.793	4.895
5.408	5.169	-0.008	8.099	14.812	8.585
5.415	3.537	3.796	6.868	4.759	5.059
19.684	31.772	12.458	17.37	23.349	18.703
12.459	42.237	7.683	35.377	44.236	20.737
10.471	24.704	4.766	13.33	17.405	14.988
7.514	23.552	8.159	13.451	15.953	16.97
12.884	31.914	10.901	12.422	11.359	12.354
0.157	0.625	0.018	0.894	6.87	1.815
8.053	8.149	6.202	14.277	11.647	12.666
-0.257	8.768	0.189	5.061	5.983	1.441
7.9	18.025	21.852	9.696	20.091	7.993
6.846	15.286	12.305	21.244	17.661	5.137
6.714	22.034	4.115	10.802	8.789	18.559
3.912	6.723	6.625	7.391	9.898	7.648
6.196	7.696	6.934	12.962	13.428	6.599
7.533	5.987	3.485	7.211	13.27	5.602
11.58	6.05	14.257	14.384	15.368	39.581
12.42	16.148	6.942	12.899	15.383	14.676
18.408	13.723	15.549	23.07	38.716	16.793
14.598	7.74	11.784	10.189	8.435	-1.006
5.271	6.565	6.53	9.29	6.177	0.732
-8.417	-6.198	-6.042	5.182	2.088	-7.324
6.732	8.044	4.779	7.343	12.078	8.25
9.095	8.172	8.477	12.085	5.953	23.092
-0.191	13.834	-2.617	3.375	2.356	0.146
2.945	11.597	-2.515	5.186	4.076	2.538
6.473	10.782	-0.07	10.608	19.106	3.696
3.872	0.323	4.639	1.202	12.521	7.844
-5.271	7.208	6.926	16.267	5.406	-0.659
4.333	10.594	8.12	5.517	7.186	3.581

FIG. 18 (Continued)

driver_gain_19p13.3	driver_loss_1q21.3	driver_loss_1q42.13	driver_loss_2p11.2	driver_loss_2q31.1
12.49	9.333	11.829	7.706	9.413
2.83	2.088	16.543	-0.148	1.633
7.002	9.123		8.906	6.55
10.744	4.379	8.782	-0.91	8.099
3.385	4.897	8.644	6.474	4.219
6.955	6.972		6.414	6.516
5.461	5.401	14.554	7.596	6.466
19.823	15.597	25.789	16.071	19.126
15.835	15.821	24.331	9.463	14.012
11.468	13.2	18.058	15.239	10.879
13.463	14.018	5.792	12.577	11.145
11.289	12.142	30.906	8.095	11.224
1.086	2.195	6.489	0.691	0.088
11.308	14.276		5.578	11.4
3.89	3.232	-5.462	-0.108	1.834
12.548	15.651	8.085	11.587	18.088
14.184	8.783	10.057	8.497	7.345
8.51	12.104	6.712	9.541	9.101
7.456	3.832	7.175	4.375	3.709
9.497	7.023	4.539	6.491	5.391
5.906	9.941	-0.191	11.678	5.542
12.388	19.639	11.453	21.68	16.097
13.883	17.479	16.211	10.06	16.321
22.37	22.976	15.775	23.224	18.501
9.335	5.504	27.051	16.669	13.727
7.274	5.451	11.303	7.423	6.331
-6.186	-4.531		-8.417	-6.267
7.839	8.65		4.882	8.667
6.929	14.557	17.404	5.673	10.432
4.179	8.547		5.516	-0.712
2.75	5.107	2.945	3.48	4.136
4.477	4.361	10.263	7.32	3.537
3.285	4.623	4.547	0.763	4.578
3.945	0.316	7.518	-3.675	1.665
5.76	5.683		7.536	7.365

FIG. 18 (Continued)

driver_loss_3p21.31	driver_loss_3p13	driver_loss_5p15.33	driver_loss_7p22.2
10.404	14.599	9.413	10.709
1.309	13.617	2.042	3.294
6.785	-8.843	7.945	8.677
5.168	29.258	4.34	4.34
5.7	7.596	5.27	4.962
7.553	7.374	6.742	7.639
5.401	6.209	7.125	7.544
17.37	25.789	19.126	18.703
29.405	3.743	13.621	14.349
15.03	-2.871	12.135	13.259
13.451	14.615	11.145	13.669
12.567	25.965	10.944	10.944
0.198	3.98	1.691	2.462
12.273	6.773	13.396	14.276
2.472	-3.554	1.963	3.232
8.737	10.189	15.651	15.651
5.747	13.423	6.759	8.412
12.398	11.126	9.547	9.512
6.775	10.577	1.27	3.832
6.176	3.367	5.108	7.113
5.039	3.075	6.787	9.941
39.581	5.089	26.523	19.411
12.899	7.722	17.383	17.847
23.07	15.775	18.501	17.744
5.771	13.914	11.401	10.233
1.978	7.014	7.121	7.798
-3.088	-4.096	-8.18	-5.078
8.853	10.91	9.92	8.597
14.04	16.323	11.938	13.028
1.112	-1.368	6.207	8.547
3.54	2.467	6.285	5.107
7.005	8.846	4.661	3.919
3.95	0.191	3.795	3.912
0.668	0.768	0.668	1.633
5.358	6.522	7.365	5.683

FIG. 18 (Continued)

driver_loss_9q34.3	driver_loss_10p12.2	driver_loss_10q24.2	driver_loss_10q24.32
10.654	9.413	12.521	14.199
4.082	1.633	2.515	2.254
3.011	6.55	4.92	-1.273
1.522	8.099	14.729	20.181
3.923	4.219	5.539	10.878
6.907	6.516	6.338	5.847
5.415	6.466	5.865	3.987
20.517	19.126	18.29	16.018
19.253	14.012	11.573	5.687
12.025	10.879	8.7	-1.667
5.897	11.145	14.359	20.871
22.909	11.224	10.275	8.373
3.98	0.088	1.691	2.766
7.143	11.4	10.891	2.223
0.591	1.834	2.077	0.958
5.623	18.088	18.551	10.201
12.583	7.345	10.492	10.224
6.823	9.101	11.126	20.978
5.134	3.709	5.262	23.359
4.915	5.391	4.612	-12.161
3.445	5.542	8.134	9.222
16.847	16.097	11.962	12.176
11.049	16.321	16.321	9.925
16.973	18.501	18.501	23.381
15.715	13.727	9.162	-7.105
6.072	6.331	7.329	-0.071
-12.143	-6.267	-6.267	-22.699
9.326	8.667	8.57	8.64
12.415	10.432	8.075	8.128
-2.401	-0.712	1.086	-1.368
0.045	4.136	2.978	1.96
7.722	3.537	2.861	1.778
4.936	4.578	3.91	-1.079
-6.329	1.665	6.336	5.581
0.209	7.365	11.991	6.522

FIG. 18 (Continued)

driver_loss_11q22.3	driver_loss_12p13.31a	driver_loss_13q14.13	driver_loss_13q14.3
6.965	9.413	11.624	12.671
2.303	2.042	2.612	3.076
5.739	7.945	6.065	6.373
5.296	4.34	12.133	8.578
2.217	5.27	6.468	5.925
6.038	6.742	9.313	7.916
6.209	7.125	5.851	5.383
19.839	19.126	20.766	19.578
28.615	13.621	32.519	24.607
10.597	12.135	16.458	13.912
11.268	11.145	11.426	12.94
15.012	10.944	16.971	14.155
0.108	1.691	2.06	1.821
9.918	13.396	18.475	14.698
0.225	1.963	10.175	5.154
12.422	15.651	14.257	12.57
9.205	6.759	13.135	14.587
6.712	9.547	11.485	9.583
4.818	1.27	4.862	4.665
8.168	5.108	8.342	7.451
7.796	6.787	10.786	8.78
12.32	26.523	20.934	17.075
12.42	17.383	14.078	13.064
20.102	18.501	25.083	23.717
17.861	11.401	10.187	9.037
6.581	7.121	8.235	7.041
-5.895	-8.18	-0.6	-3.122
6.744	9.92	14.171	10.818
9.968	11.938	13.851	10.321
-0.191	6.207	4.127	3.457
1.5	6.285	5.255	3.229
6.473	4.661	8.86	7.8
4.809	3.795	9.192	8.143
-0.016	0.668	12.836	3.832
5.765	7.365	7.03	6.322

FIG. 18 (Continued)

driver_loss_14q32.12	driver_loss_16q22.1	driver_loss_17p13.3	driver_loss_17p13.1
10.988	10.709	9.413	10.352
2.612	2.22	2.042	9.967
6.503	7.945	7.945	22.919
2.861	8.099	4.34	27.328
5.541	5.649	5.649	12.569
8.006	6.742	6.742	7.726
7.204	6.229	7.204	8.316
21.838	20.223	17.36	33.439
13.653	13.621	13.621	38.535
15.247	9.612	12.135	31.314
13.32	12.069	11.145	38.757
9.793	9.214	10.944	34.548
-0.271	1.691	1.691	0.935
7.49	10.406	13.396	9.421
0.449	1.048	1.963	6.969
1.437	15.177	15.651	10.631
5.076	7.224	6.759	20.329
11.327	6.63	8.98	31.599
2.889	3.832	1.27	9.671
2.398	6.736	5.002	18.414
3.652	10.904	8.81	1.83
36.025	18.524	26.523	5.701
16.3	16.519	17.383	18.469
14.63	25.253	24.118	11.271
10.501	10.115	11.401	20.459
5.451	7.32	7.121	3.168
-9.647	-8.18	-8.18	-6.747
9.023	8.667	9.92	6.081
13.111	10.118	11.938	7.563
-1.725	4.179	6.207	16.733
5.186	1.537	4.317	8.188
3.949	4.013	4.013	8.801
3.797	3.795	3.795	0.403
-2.976	0.668	0.668	12.181
4.767	5.76	7.365	5.695

FIG. 18 (Continued)

driver_tri_12	driver_gain_2p
14.575	7.706
5.355	-0.148
9.987	8.906
8.404	-0.91
13.396	6.474
9.388	6.414
7.891	7.596
22.983	16.071
17.121	9.463
14.809	15.239
22.462	12.577
17.566	8.095
2.877	0.691
16.697	5.578
9.694	-0.108
9.828	11.587
20.612	8.497
10.676	9.541
7.847	4.375
16.174	6.491
8.395	11.678
8.858	21.68
18.502	10.06
16.927	23.224
8.232	16.669
9.965	7.423
-2.554	-8.417
8.849	4.882
12.826	5.673
12.658	5.516
7.524	3.48
4.742	7.32
-0.092	0.763
5.574	-3.675
6.78	7.536

FIG. 18 (Continued)

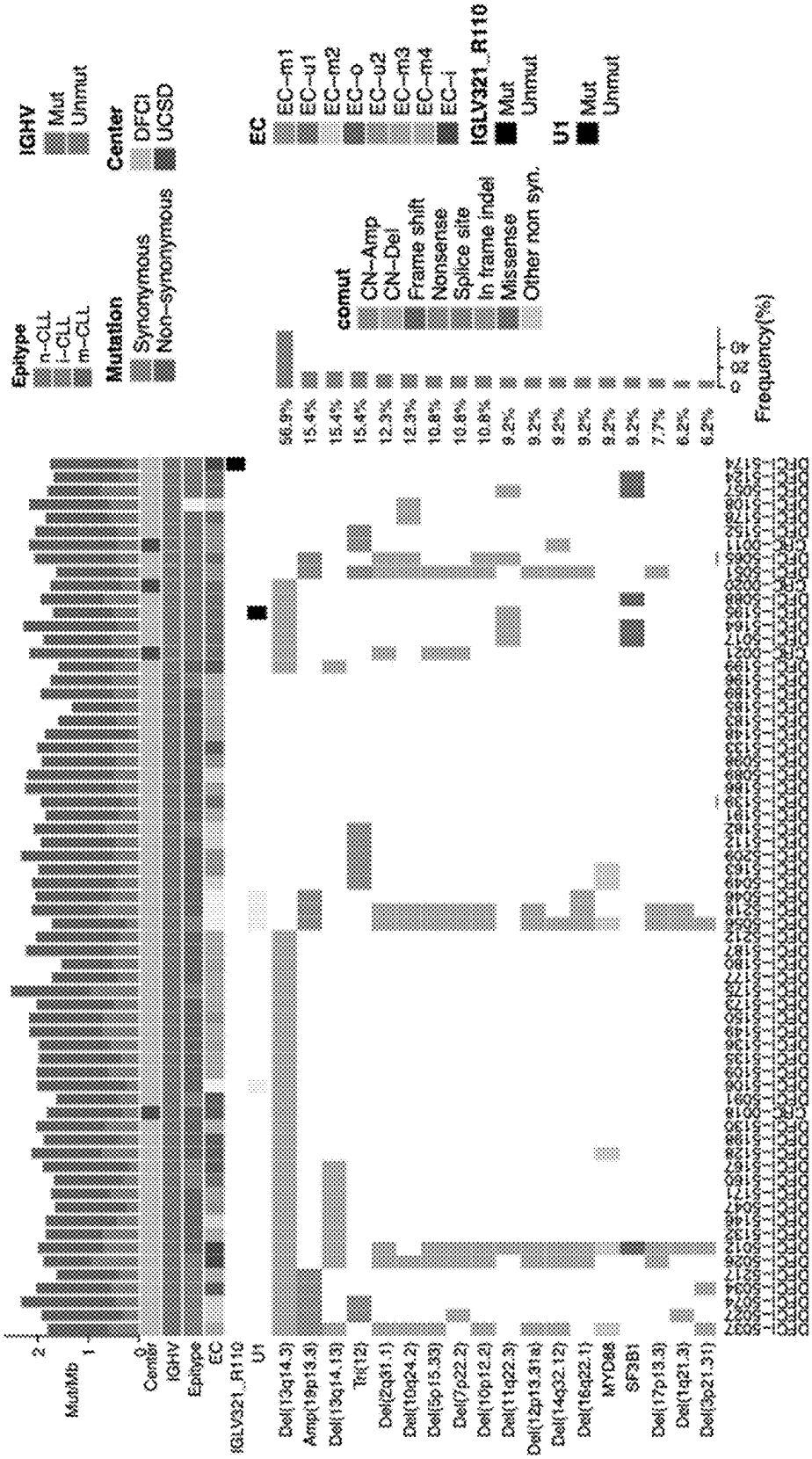

Epitype
n-CLL
i-CLL
m-CLL
Mutation
Synonymous
Non-synonymous
IGHV
Mut
Unmut
Center
DFCI
UCSD
EC
EC-m1
EC-u1
EC-m2
EC-o
EC-u2
EC-m3
EC-m4
EC-i
IGLV321_R110
Mut
Unmut
U1
Mut
Unmut
comut
CN-Amp
CN-Del
Frame shift
Nonsense
Splice site
In frame indel
Missense
Other non syn.
Frequency(%)
MutMb
Center
IGHV
Epitype
EC
IGLV321_R110
U1
Del(13q14.3)
Amp(18p13.3)
Del(13q14.13)
Tri(12)
Del(2q31.1)
Del(10q24.2)
Del(5p15.33)
Del(7p22.2)
Del(10p12.2)
Del(11q22.3)
Del(12p13.31a)
Del(14q32.12)
Del(16q22.1)
MYD88
SF3B1
Del(17p13.3)
Del(1q21.3)
Del(3p21.31)

FIG. 19

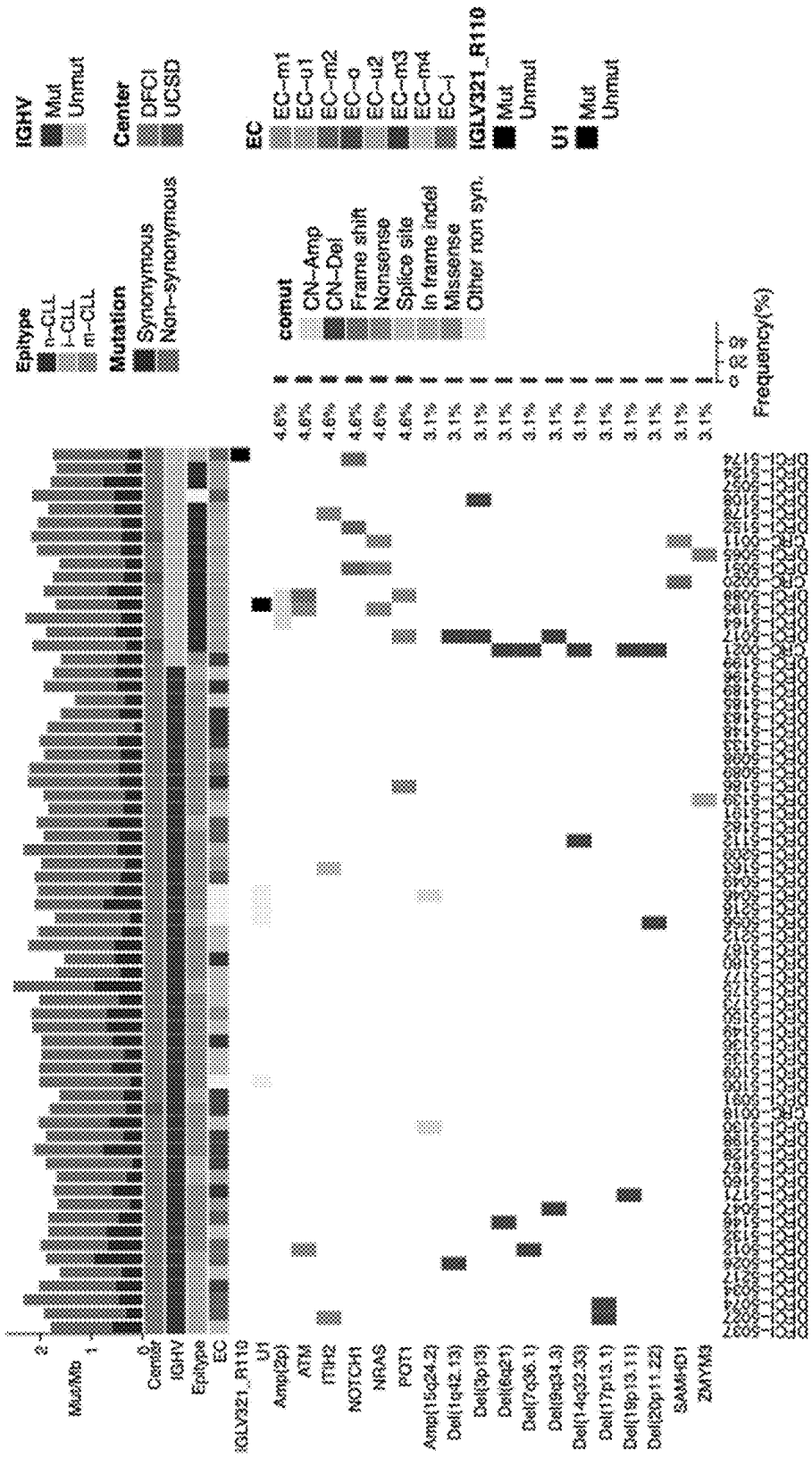


FIG. 19 (Continued)

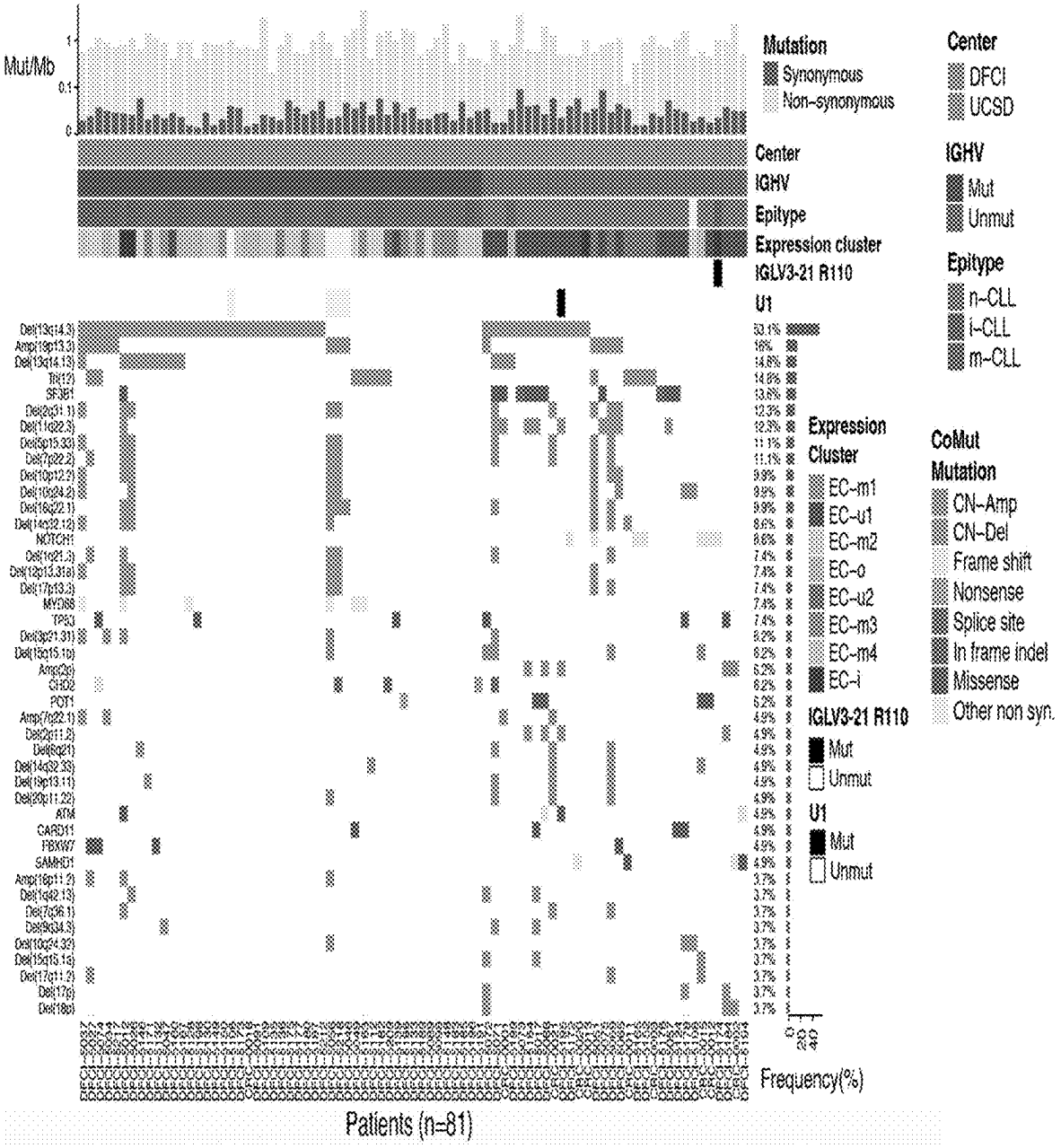

Mut/Mb
Mutation
Synonymous
Non-synonymous
Center
DFCI
UCSD
Center
IGHV
Epitype
Expression cluster
IGLV3-21 R110
U1
IGHV
Mut
Unmut
Epitype
n-CLL
i-CLL
m-CLL
Expression Cluster
EC-m1
EC-u1
EC-m2
EC-o
EC-u2
EC-m3
EC-m4
EC-i
IGLV3-21 R110
Mut
Unmut
U1
Mut
Unmut
CoMut Mutation
CN-Amp
CN-Del
Frame shift
Nonsense
Splice site
In frame indel
Missense
Other non syn.
Frequency(%)
Patients (n=81)

FIG. 20

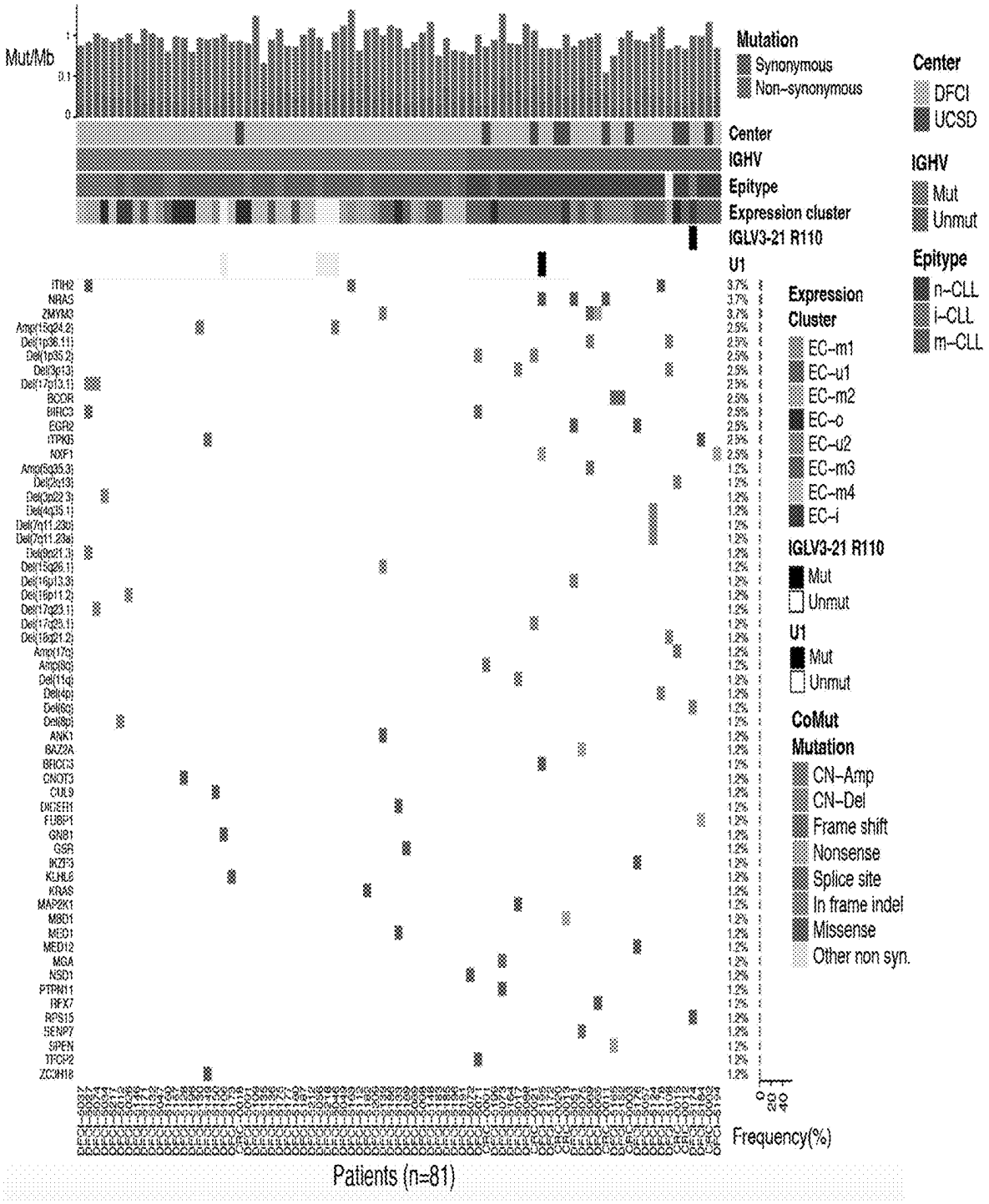


FIG. 20 (Continued)

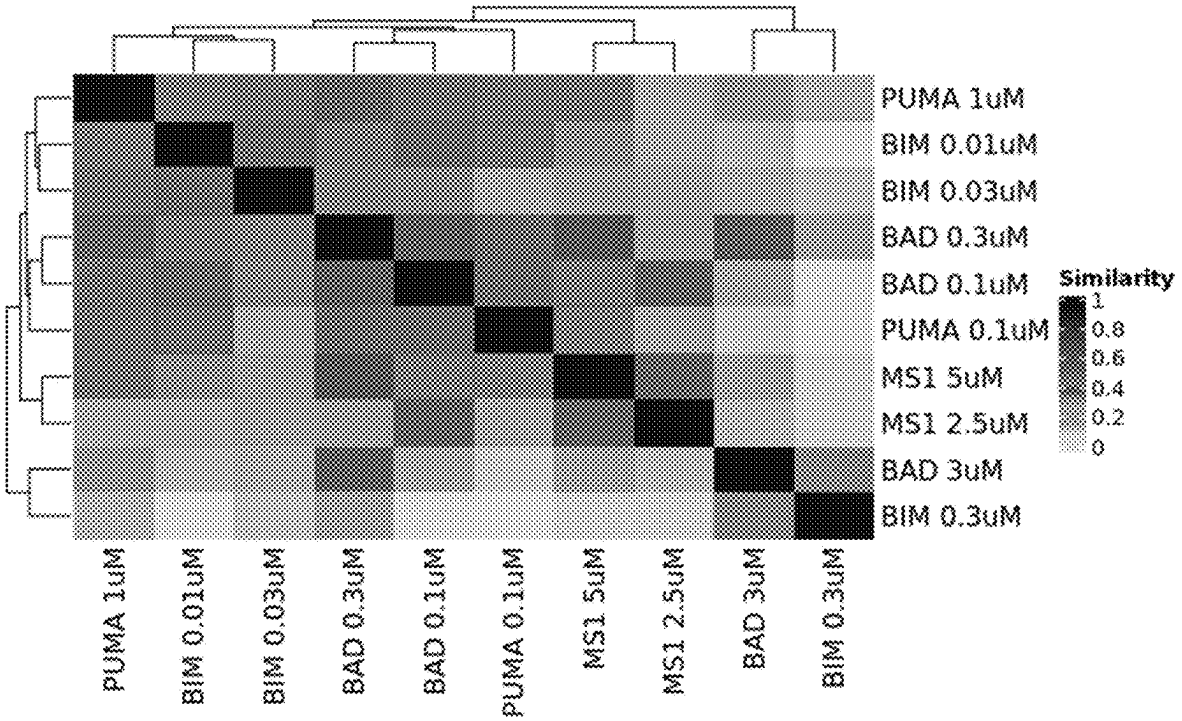

PUMA 1uM
BIM 0.01uM
BIM 0.03uM
BAD 0.3uM
BAD 0.1uM
PUMA 0.1uM
MS1 5uM
MS1 2.5uM
BAD 3uM
BIM 0.3uM
Similarity
1
0.8
0.6
0.4
0.2
0

FIG. 21A

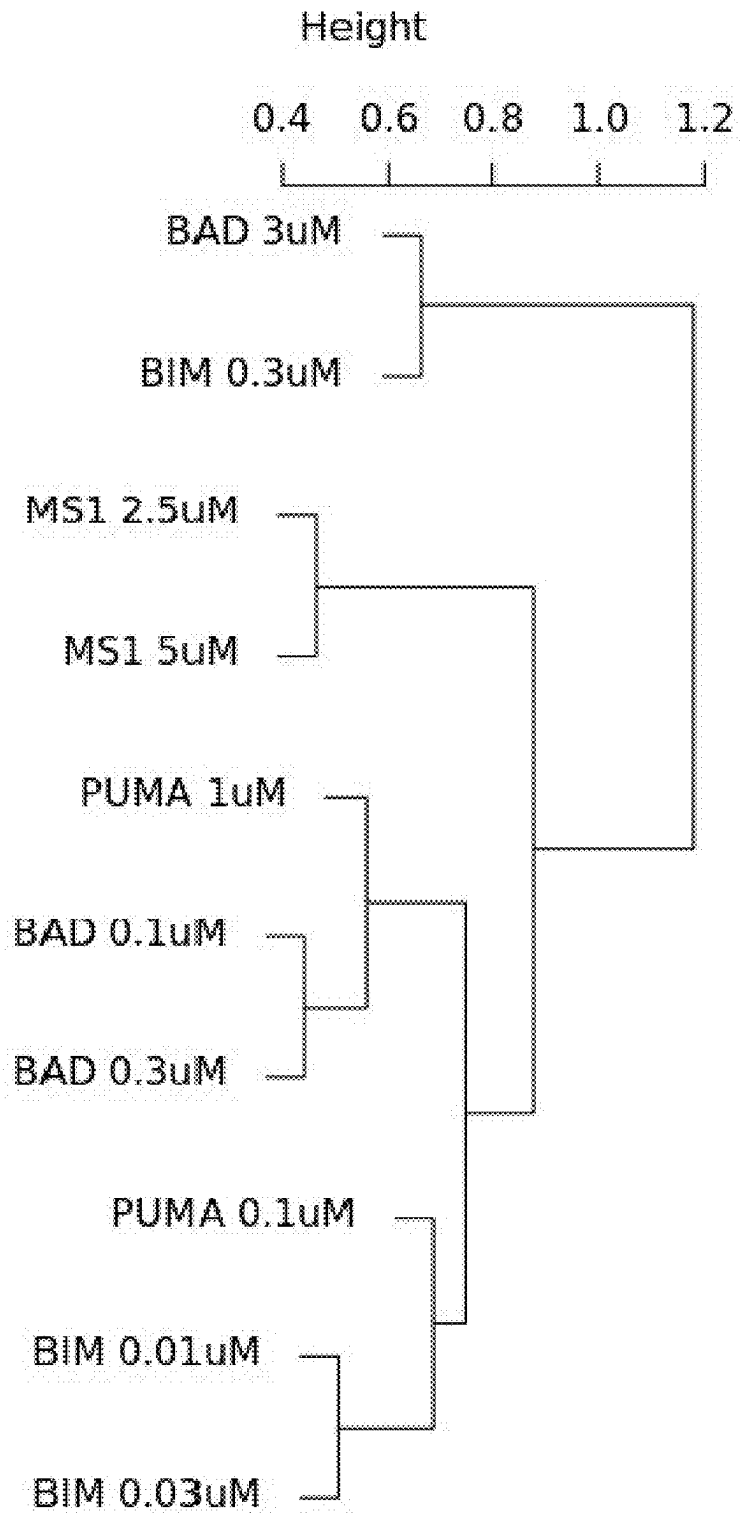

Height
0.4
0.6
0.8
1.0
1.2
BAD 3uM
BIM 0.3uM
MS1 2.5uM
MS1 5uM
PUMA 1uM
BAD 0.1uM
BAD 0.3uM
PUMA 0.1uM
BIM 0.01uM
BIM 0.03uM

FIG. 21B

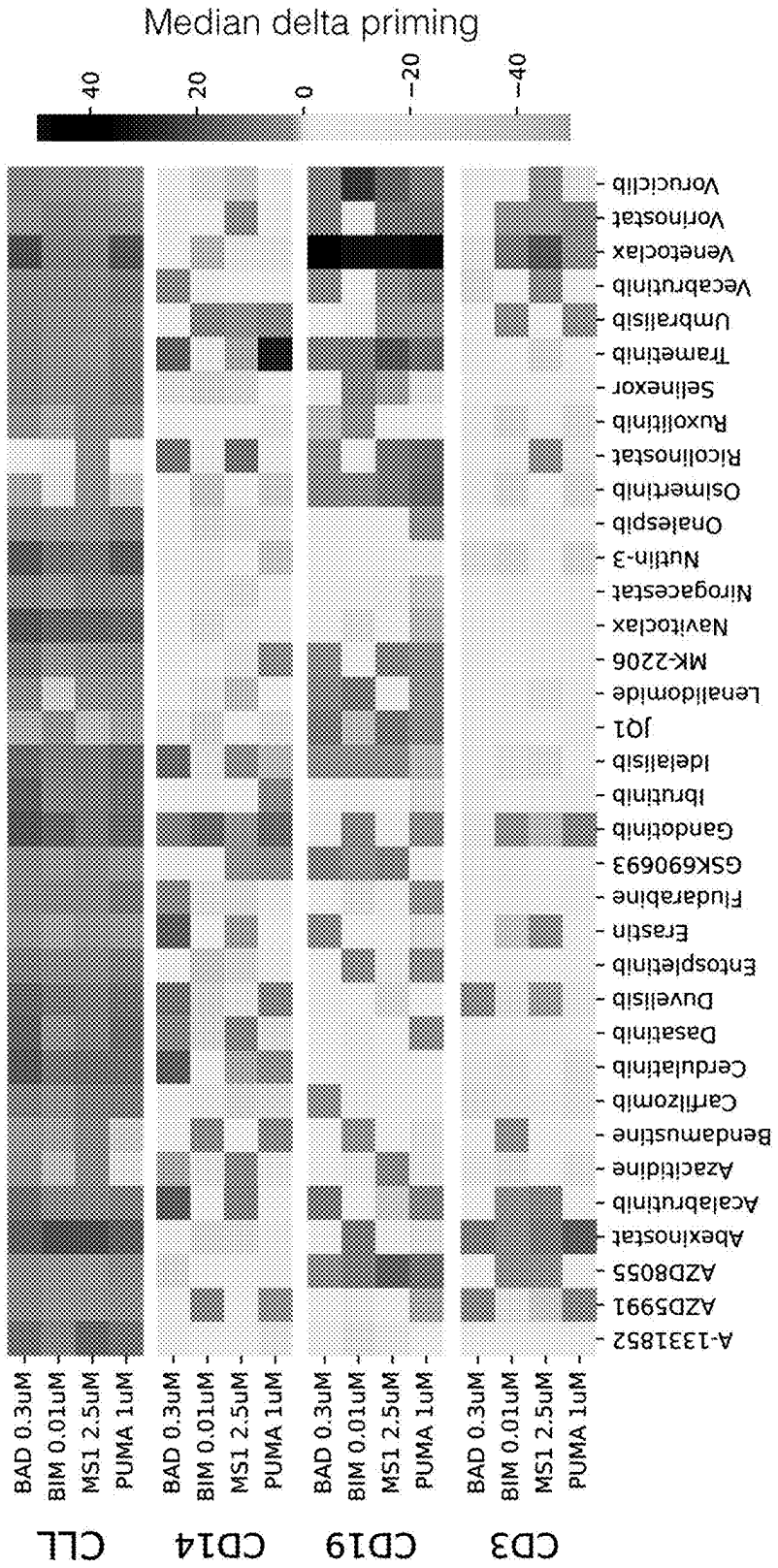

Median delta priming
40
20
0
−20
−40
CLL
CD14
CD19
CD3
BAD 0.3uM
BIM 0.01uM
MS1 2.5uM
PUMA 1uM
A-1331852
AZD5991
AZD8055
Abexinostat
Acalabrutinib
Azacitidine
Bendamustine
Carfilzomib
Cerdulatinib
Dasatinib
Duvelisib
Entospletinib
Erastin
Fludarabine
GSK690693
Gandotinib
Ibrutinib
Idelalisib
JQ1
Lenalidomide
MK-2206
Navitoclax
Nirogacestat
Nutlin-3
Onalespib
Osimertinib
Ricolinostat
Ruxolitinib
Selinexor
Trametinib
Umbralisib
Venetoclax
Vorinostat
Voruciclib

FIG. 22A

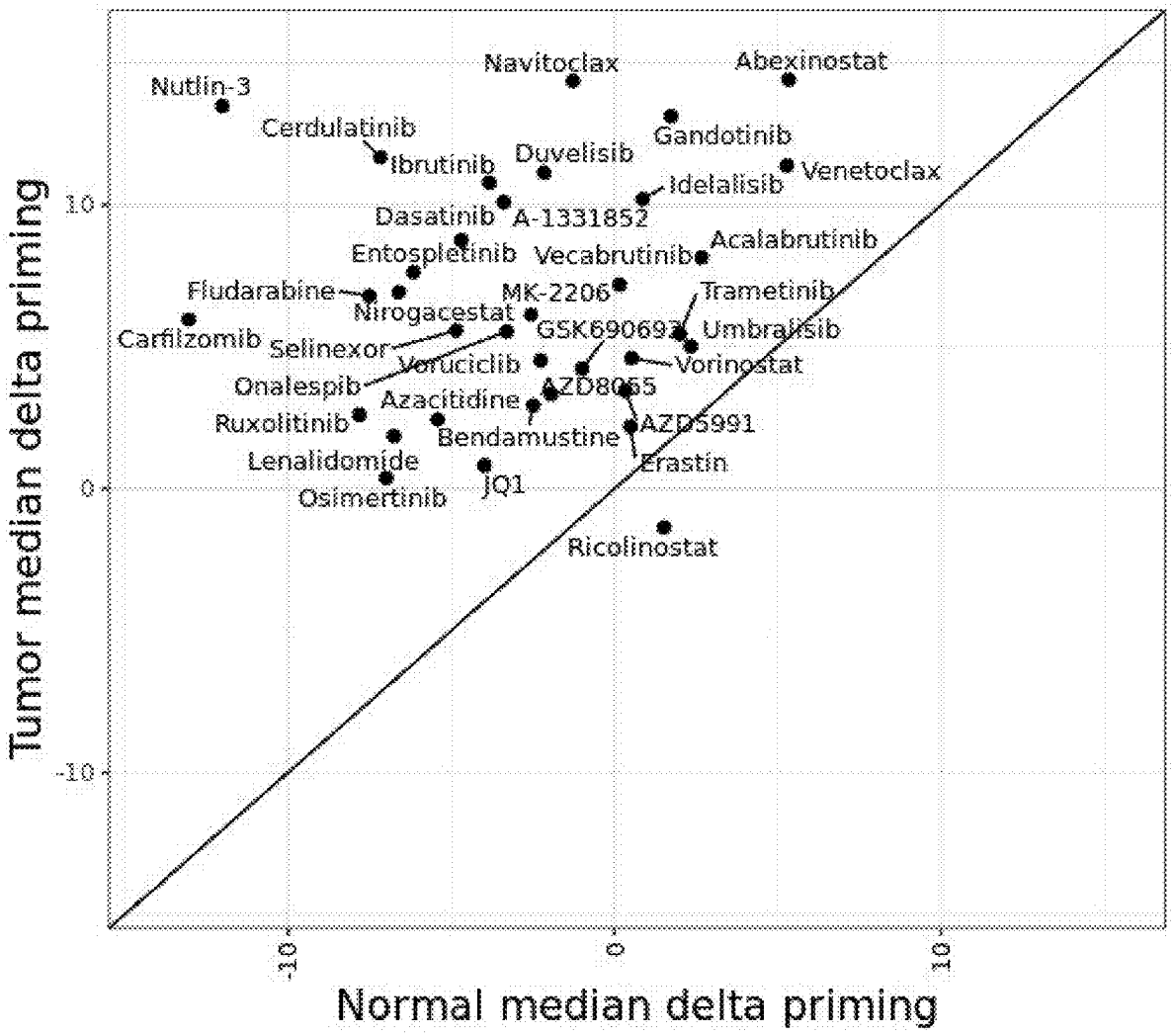

Navitoclax
Abexinostat
Nutlin-3
Cerdulatinib
Gandotinib
Duvelisib
Ibrutinib
Venetoclax
Idelalisib
Dasatinib
A-1331852
Acalabrutinib
Entospletinib
Vecabrutinib
Fludarabine
MK-2206
Trametinib
Nirogacestat
Carfilzomib
GSK690693
Umbralisib
Selinexor
Voruciclib
Vorinostat
Onalespib
AZD8055
Azacitidine
Ruxolitinib
AZD5991
Bendamustine
Lenalidomide
Erastin
JQ1
Osimertinib
Ricolinostat
Tumor median delta priming
Normal median delta priming
10
0
-10
-10
0
10

FIG. 22B

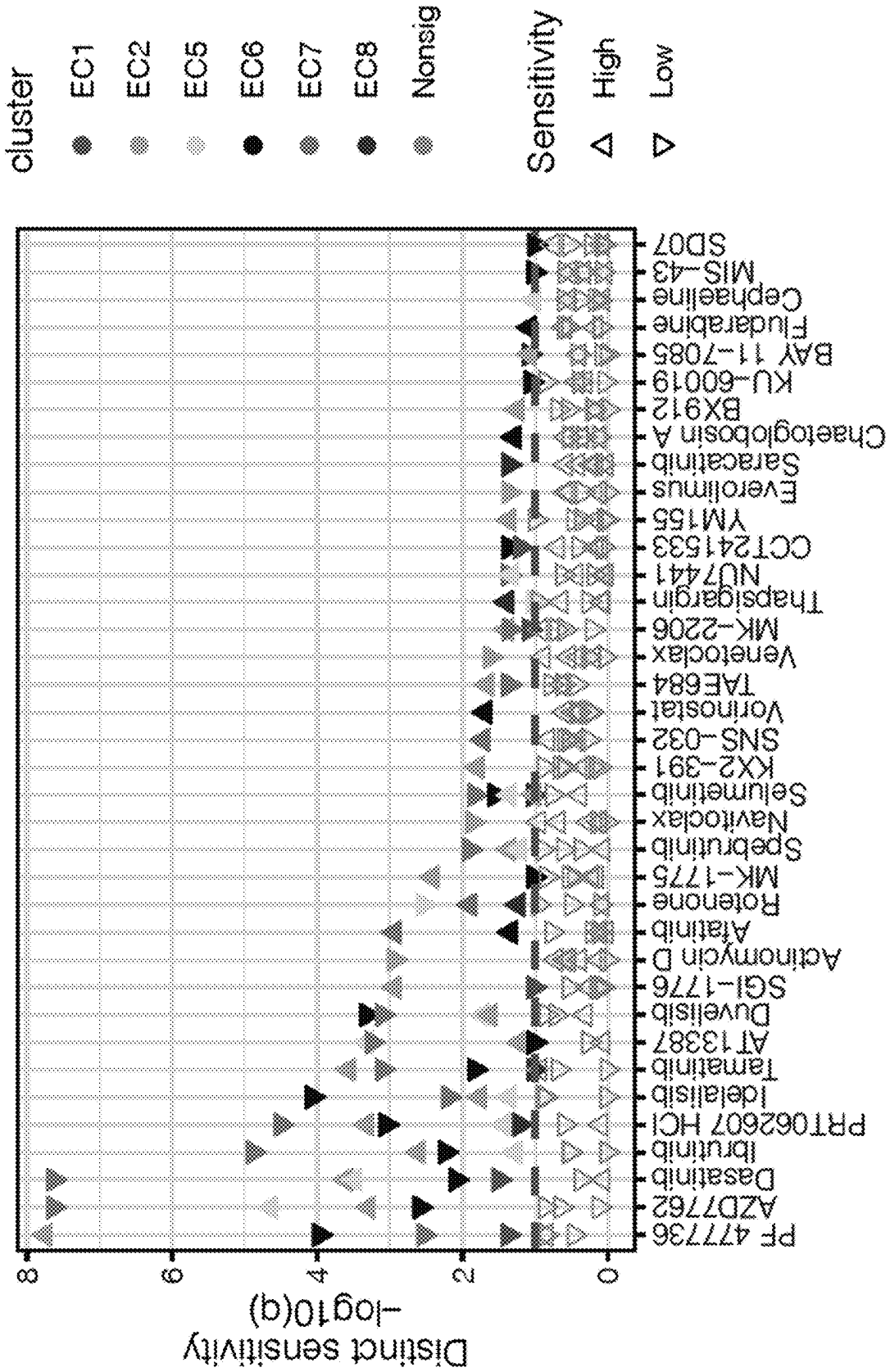

cluster
EC1
EC2
EC5
EC6
EC7
EC8
Nonsig
Sensitivity
High
Low
Distinct sensitivity
-log10(q)
8
6
4
2
0
PF 477736
AZD7762
Dasatinib
Ibrutinib
PRT062607 HCl
Idelalisib
Tamatinib
AT13387
Duvelisib
SGI-1776
Actinomycin D
Afatinib
Rotenone
MK-1775
Speburtinib
Navitoclax
Selumetinib
KX2-391
SNS-032
Vorinostat
TAE684
Venetoclax
MK-2206
Thapsigargin
NU7441
CCT241533
YM155
Everolimus
Saracatinib
Chaetoglobosin A
BX912
KU-60019
BAY 11-7085
Fludarabine
Cephaeline
MIS-43
SD07

FIG. 23

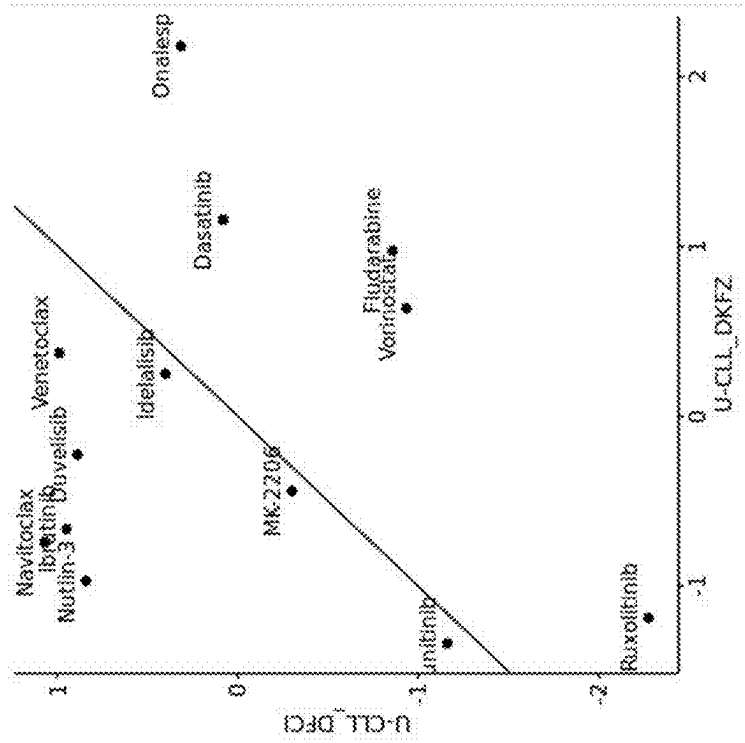


FIG. 24B

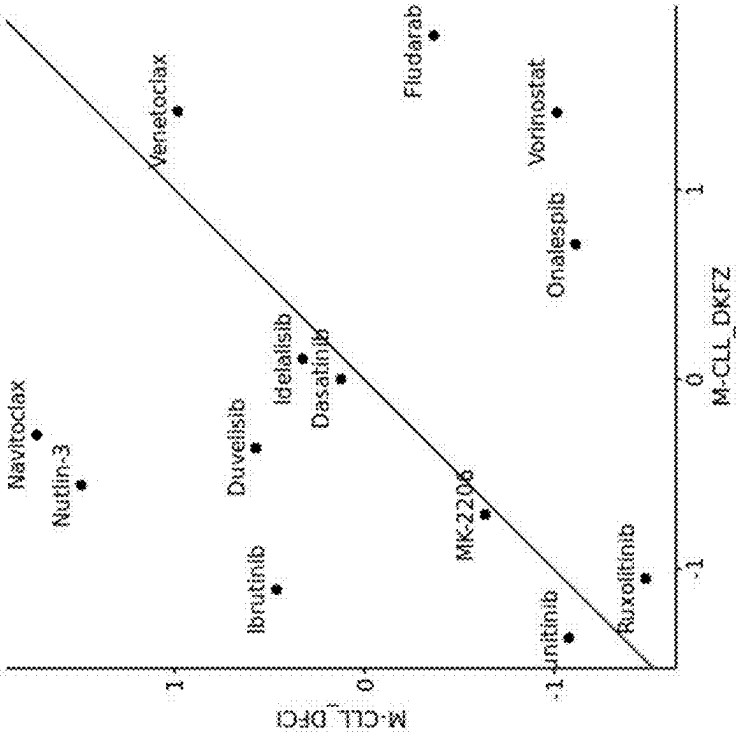


FIG. 24A

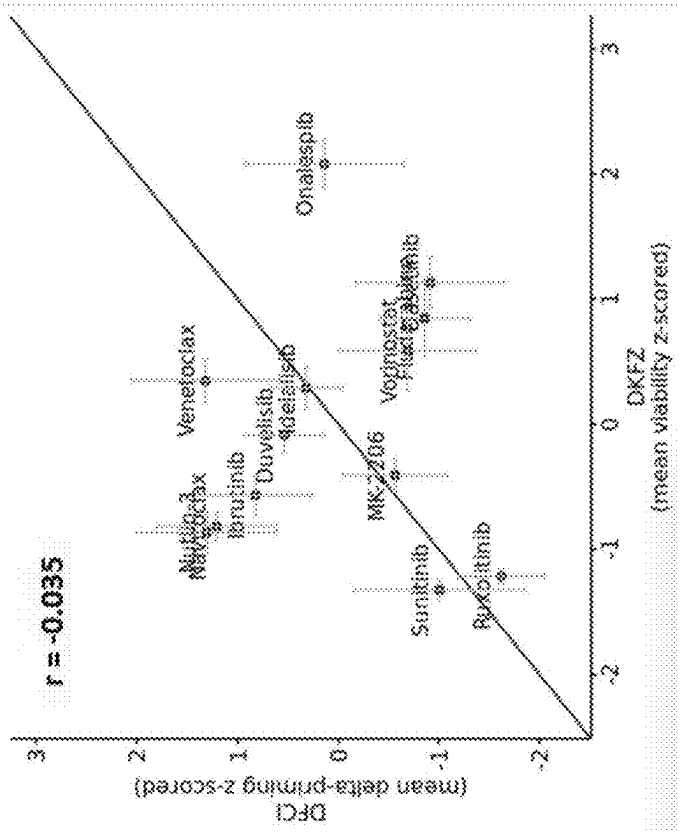


FIG. 24D

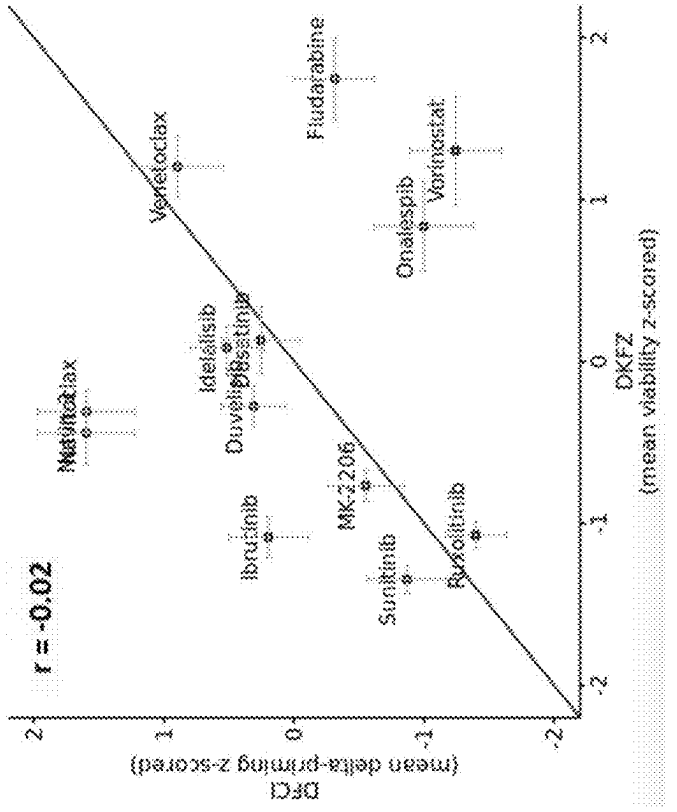


FIG. 24C

	peptide	drug	feature	direction	dprim_median_diff	dprim_median_driver_1
1319	peptide_BAD 0.3uM	drug_name_Venetoclax	ec_name_EC-m3	Sensitive	23.353812	43.150455
1329	peptide_MS1 2.5uM	drug_name_Venetoclax	driver_gain_16p11.2	Sensitive	22.124329	31.181162
1317	peptide_BAD 0.3uM	drug_name_Venetoclax	driver_loss_13q14.3	Sensitive	13.084143	22.497470
1311	peptide_MS1 2.5uM	drug_name_Venetoclax	driver_loss_13q14.13	Sensitive	10.086182	17.006196
1340	peptide_PUMA 1uM	drug_name_Venetoclax	driver_tri_12	Resistant	-17.576560	1.992989
1340	peptide_BAD 0.3uM	drug_name_Venetoclax	driver_tri_12	Resistant	-18.875257	2.262609
1338	peptide_BAD 0.3uM	drug_name_Venetoclax	ec_name_EC-m2	Resistant	-20.048727	0.545074
1338	peptide_PUMA 1uM	drug_name_Venetoclax	ec_name_EC-m2	Resistant	-20.218382	-0.151773

FIG. 25

peptide	drug	feature	direction	dprim_median_diff	dprim_median_driver_1
peptide_BAD 0.3uM	drug_name_Zanubrutinib	driver_tri_12	Sensitive	17.639026	24.723658
peptide_BIM 0.01uM	drug_name_Acalabrutinib	driver_tri_12	Sensitive	13.693430	18.694885
peptide_BIM 0.01uM	drug_name_Zanubrutinib	driver_tri_12	Sensitive	11.170778	18.150598
peptide_BIM 0.01uM	drug_name_Zanubrutinib	ec_name_EC-m2	Sensitive	9.357153	16.348487
peptide_MS1 2.5uM	drug_name_Zanubrutinib	driver_gain_19p13.3	Resistant	-5.470736	1.463342
peptide_BIM 0.01uM	drug_name_Acalabrutinib	driver_loss_11q22.3	Resistant	-5.715319	1.820423
peptide_MS1 2.5uM	drug_name_Zanubrutinib	driver_FBXW7	Resistant	-6.552817	0.381261
peptide_MS1 2.5uM	drug_name_Ibrutinib	driver_loss_11q22.3	Resistant	-7.199216	3.187407
peptide_PUMA 1uM	drug_name_Zanubrutinib	driver_gain_19p13.3	Resistant	-7.472407	2.802010
peptide_BIM 0.01uM	drug_name_Zanubrutinib	ec_name_EC-m4	Resistant	-8.442787	1.917514
peptide_MS1 2.5uM	drug_name_Ibrutinib	driver_loss_10p12.2	Resistant	-8.932885	0.994411
peptide_MS1 2.5uM	drug_name_Ibrutinib	driver_loss_2q31.1	Resistant	-8.932885	0.994411
peptide_BIM 0.01uM	drug_name_Ibrutinib	driver_MYD88	Resistant	-11.186043	-2.926916
peptide_PUMA 1uM	drug_name_Zanubrutinib	driver_loss_1q21.3	Resistant	-11.450247	-1.187031
peptide_PUMA 1uM	drug_name_Zanubrutinib	driver_loss_7p22.2	Resistant	-11.450247	-1.187031
peptide_PUMA 1uM	drug_name_Zanubrutinib	driver_loss_11q22.3	Resistant	-11.461447	-1.187031
peptide_BIM 0.01uM	drug_name_Ibrutinib	driver_loss_10p12.2	Resistant	-11.593629	-2.926916
peptide_BIM 0.01uM	drug_name_Ibrutinib	driver_loss_2q31.1	Resistant	-11.593629	-2.926916
peptide_PUMA 1uM	drug_name_Vecabrutinib	driver_loss_10q24.2	Resistant	-12.615928	-1.798652
peptide_PUMA 1uM	drug_name_Zanubrutinib	priorrrt_Post	Resistant	-12.690306	-2.421490
peptide_BAD 0.3uM	drug_name_Ibrutinib	driver_MYD88	Resistant	-13.607066	3.021473
peptide_PUMA 1uM	drug_name_Zanubrutinib	driver_FBXW7	Resistant	-13.919165	-3.655949
peptide_BAD 0.3uM	drug_name_Zanubrutinib	priorrrt_Post	Resistant	-17.323697	-5.967234
peptide_PUMA 1uM	drug_name_Ibrutinib	driver_loss_14q32.12	Resistant	-20.961022	-7.419343

FIG. 26

peptide	drug	feature	direction	dprim_median_diff	dprim_median_driver_1
peptide_BIM 0.01uM	drug_name_Abexinostat	priortrt_Post	Sensitive	34.082488	51.315562
peptide_MS1 2.5uM	drug_name_Abexinostat	priortrt_Post	Sensitive	34.422107	48.872546
peptide_BIM 0.01uM	drug_name_A-1331852	priortrt_Post	Resistant	-12.030084	-2.064177
peptide_MS1 2.5uM	drug_name_Crizotinib	priortrt_Post	Resistant	-13.862708	-15.154680
peptide_PUMA 1uM	drug_name_MK-2206	priortrt_Post	Resistant	-12.375996	-4.388575
peptide_BAD 0.3uM	drug_name_MK-2206	priortrt_Post	Resistant	-12.251718	0.869943
peptide_MS1 2.5uM	drug_name_MK-2206	priortrt_Post	Resistant	-12.759233	-5.375226
peptide_PUMA 1uM	drug_name_Nutlin-3	priortrt_Post	Resistant	-19.399423	0.068959
peptide_BIM 0.01uM	drug_name_Nutlin-3	priortrt_Post	Resistant	-10.100519	3.540045
peptide_BAD 0.3uM	drug_name_Nutlin-3	priortrt_Post	Resistant	-15.247612	4.709402
peptide_PUMA 1uM	drug_name_Ponatinib	priortrt_Post	Resistant	-24.830947	-24.135829
peptide_BIM 0.01uM	drug_name_Ponatinib	priortrt_Post	Resistant	-11.281109	-11.489096
peptide_MS1 2.5uM	drug_name_Ponatinib	priortrt_Post	Resistant	-22.719427	-22.205576
peptide_PUMA 1uM	drug_name_Rapamycin	priortrt_Post	Resistant	-8.049202	0.586371
peptide_BAD 0.3uM	drug_name_Rapamycin	priortrt_Post	Resistant	-17.944963	-7.363071
peptide_MS1 2.5uM	drug_name_Rapamycin	priortrt_Post	Resistant	-20.249892	-8.605907
peptide_MS1 2.5uM	drug_name_Sorafenib	priortrt_Post	Resistant	-8.231161	-10.887598
peptide_BAD 0.3uM	drug_name_Sunitinib	priortrt_Post	Resistant	-10.821031	-4.775608
peptide_PUMA 1uM	drug_name_Zanubrutinib	priortrt_Post	Resistant	-12.690306	-2.421490
peptide_BAD 0.3uM	drug_name_Zanubrutinib	priortrt_Post	Resistant	-17.323697	-5.967234

FIG. 27

peptide	drug	feature	direction	dprim_median_diff	dprim_median_driver_1
peptide_BAD 0.3uM	drug_name_Abexinostat	ec_name_EC-m2	Sensitive	37.169331	61.179951
peptide_BAD 0.3uM	drug_name_Navitoclax	driver_loss_14q32.12	Sensitive	25.479619	44.005213
peptide_BAD 0.3uM	drug_name_Cerdulatinib	driver_loss_13q14.3	Sensitive	24.463491	27.202581
peptide_BAD 0.3uM	drug_name_AZD5991	ec_name_EC-1	Sensitive	24.148171	29.974307
peptide_BAD 0.3uM	drug_name_AZD5991	driver_loss_14q32.12	Sensitive	24.148171	29.974307
peptide_BAD 0.3uM	drug_name_Navitoclax	driver_loss_5p15.33	Sensitive	23.425646	42.546788
peptide_BAD 0.3uM	drug_name_Navitoclax	driver_loss_12p13.31a	Sensitive	23.425646	42.546788
peptide_BAD 0.3uM	drug_name_Navitoclax	driver_loss_17p13.3	Sensitive	23.425646	42.546788
peptide_BAD 0.3uM	drug_name_Venetoclax	ec_name_EC-m3	Sensitive	23.353812	43.150455
peptide_BAD 0.3uM	drug_name_Atorvastatin	driver_FBXW7	Sensitive	21.355430	27.742161
peptide_BAD 0.3uM	drug_name_Cerdulatinib	driver_loss_13q14.13	Sensitive	19.545422	32.560847
peptide_BAD 0.3uM	drug_name_Zanubrutinib	driver_tri_12	Sensitive	17.639036	24.723658
peptide_BAD 0.3uM	drug_name_Navitoclax	ec_name_EC-m3	Sensitive	17.367767	35.658438
peptide_BAD 0.3uM	drug_name_Navitoclax	igkv_mut_mutated	Sensitive	15.631261	22.179708
peptide_BAD 0.3uM	drug_name_GSK590683	ec_name_EC-a	Sensitive	14.816048	21.417232
peptide_BAD 0.3uM	drug_name_Abexinostat	c3_epitype_m-CLL	Sensitive	14.597301	23.143269
peptide_BAD 0.3uM	drug_name_Trametinib	driver_CHD2	Sensitive	13.909253	21.433068
peptide_BAD 0.3uM	drug_name_Ponatinib	c3_epitype_m-CLL	Sensitive	13.761369	2.769285
peptide_BAD 0.3uM	drug_name_Bendamustine	driver_loss_14q32.12	Sensitive	13.585693	15.052934
peptide_BAD 0.3uM	drug_name_Venetoclax	driver_loss_13q14.3	Sensitive	13.084143	22.487470
peptide_BAD 0.3uM	drug_name_Nutlin-3	igkv_mut_mutated	Sensitive	11.766150	21.209512
peptide_BAD 0.3uM	drug_name_Bendamustine	driver_loss_5p15.33	Sensitive	11.555510	13.264119
peptide_BAD 0.3uM	drug_name_Bendamustine	driver_loss_7p22.2	Sensitive	11.555510	13.264119
peptide_BAD 0.3uM	drug_name_Bendamustine	driver_loss_12p13.31a	Sensitive	11.555510	13.264119
peptide_BAD 0.3uM	drug_name_Bendamustine	ec_name_EC-1	Sensitive	11.282835	13.264119
peptide_BAD 0.3uM	drug_name_Rapamycin	igkv_mut_mutated	Sensitive	10.383776	11.398514
peptide_BAD 0.3uM	drug_name_Atorvastatin	ec_name_EC-u1	Sensitive	10.361844	16.196162
peptide_BAD 0.3uM	drug_name_Azacitidine	driver_MYD88	Sensitive	10.047139	12.508489

FIG. 28

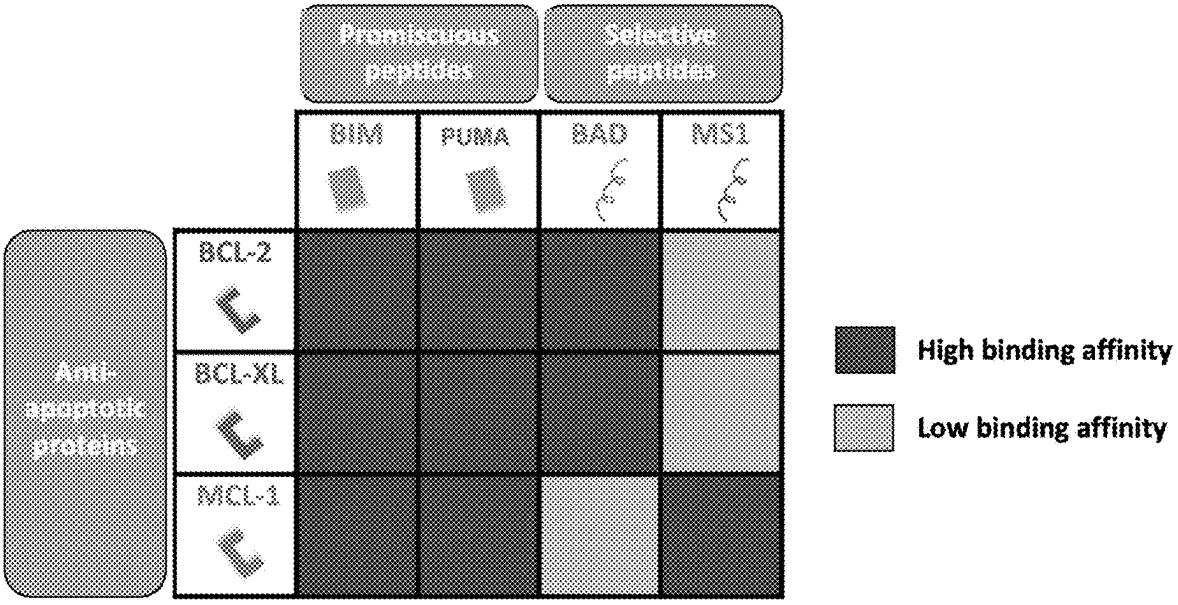

Promiscuous peptides
Selective peptides
BIM
PUMA
BAD
MS1
BCL-2
BCL-XL
MCL-1
Anti-apoptotic proteins
High binding affinity
Low binding affinity

FIG. 29

peptide	drug	feature	direction	dprim_median_diff	dprim_median_driver_1
peptide_MS1 2.5uM	drug_name_Navitoclax	driver_MYD88	Sensitive	37.543780	51.837877
peptide_MS1 2.5uM	drug_name_Navitoclax	driver_gain_16p11.2	Sensitive	37.543780	51.837877
peptide_MS1 2.5uM	drug_name_Navitoclax	driver_loss_14q32.12	Sensitive	37.543780	51.837877
peptide_MS1 2.5uM	drug_name_Abexinostat	priortrt_Post	Sensitive	34.422107	48.872546
peptide_MS1 2.5uM	drug_name_Abexinostat	driver_FBXW7	Sensitive	32.438012	46.868063
peptide_MS1 2.5uM	drug_name_Dasatinib	driver_tri_12	Sensitive	28.973943	34.705117
peptide_MS1 2.5uM	drug_name_Venetoclax	driver_gain_16p11.2	Sensitive	22.124329	31.181162
peptide_MS1 2.5uM	drug_name_Idelalisib	driver_tri_12	Sensitive	21.749642	31.414661
peptide_MS1 2.5uM	drug_name_Duvelisib	driver_CHD2	Sensitive	19.259289	26.754676
peptide_MS1 2.5uM	drug_name_Cerdulatinib	driver_loss_13q14.13	Sensitive	15.131056	26.484001
peptide_MS1 2.5uM	drug_name_Bendamustine	ec_name_EC-m3	Sensitive	14.062461	18.391336
peptide_MS1 2.5uM	drug_name_GSK690693	ec_name_EC-o	Sensitive	13.129507	16.705629
peptide_MS1 2.5uM	drug_name_Nirogacestat	ighv_mut_mutated	Sensitive	12.283921	10.036842
peptide_MS1 2.5uM	drug_name_Trametinib	driver_CHD2	Sensitive	12.136982	14.238616
peptide_MS1 2.5uM	drug_name_Rapamycin	ighv_mut_mutated	Sensitive	11.871453	11.771519
peptide_MS1 2.5uM	drug_name_Venetoclax	driver_loss_13q14.13	Sensitive	10.086182	17.006196

FIG. 30

Attorney Docket No.: 167741-050302/US/CON
Electronic Deposit Date: March 20, 2025

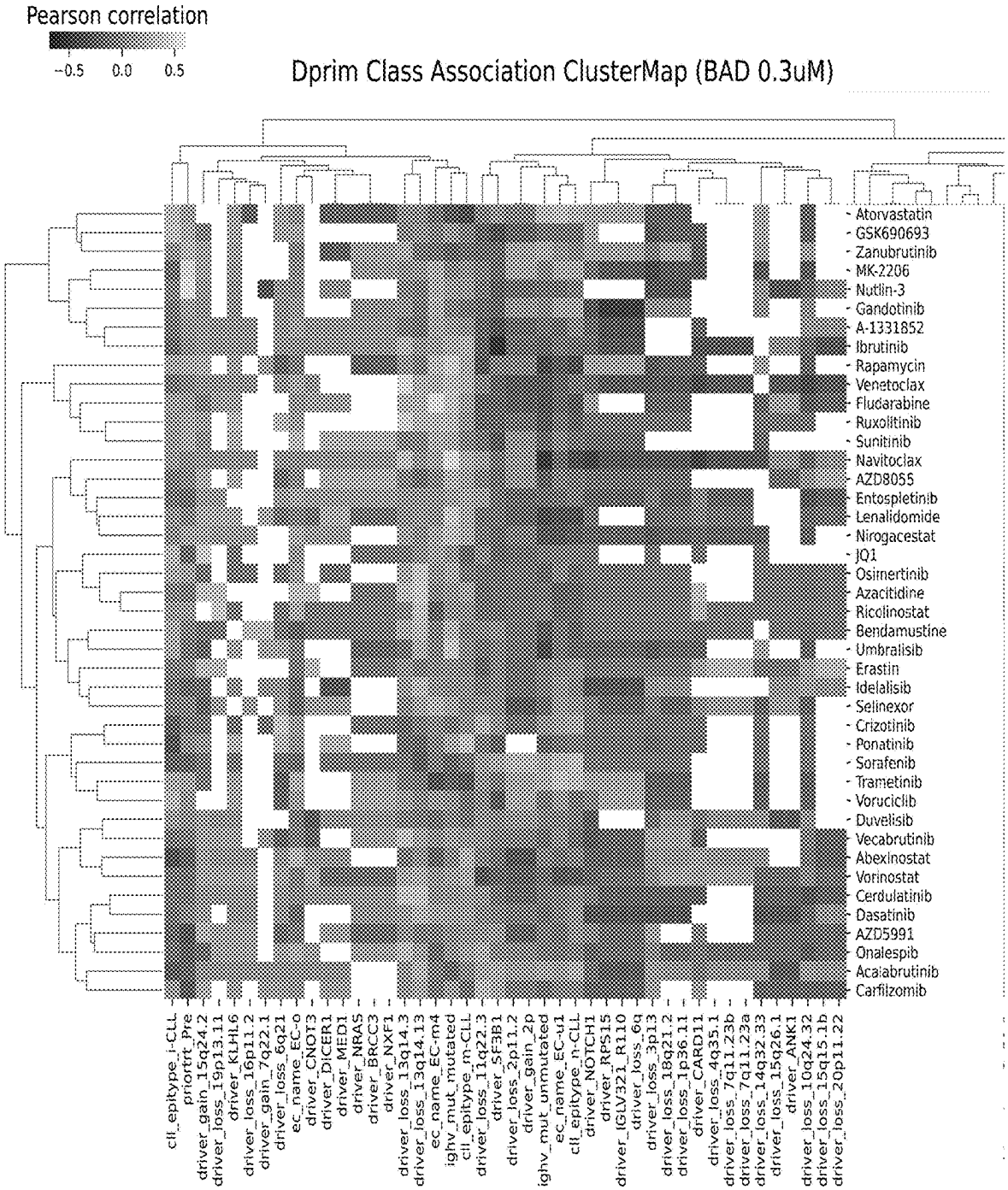


FIG. 31

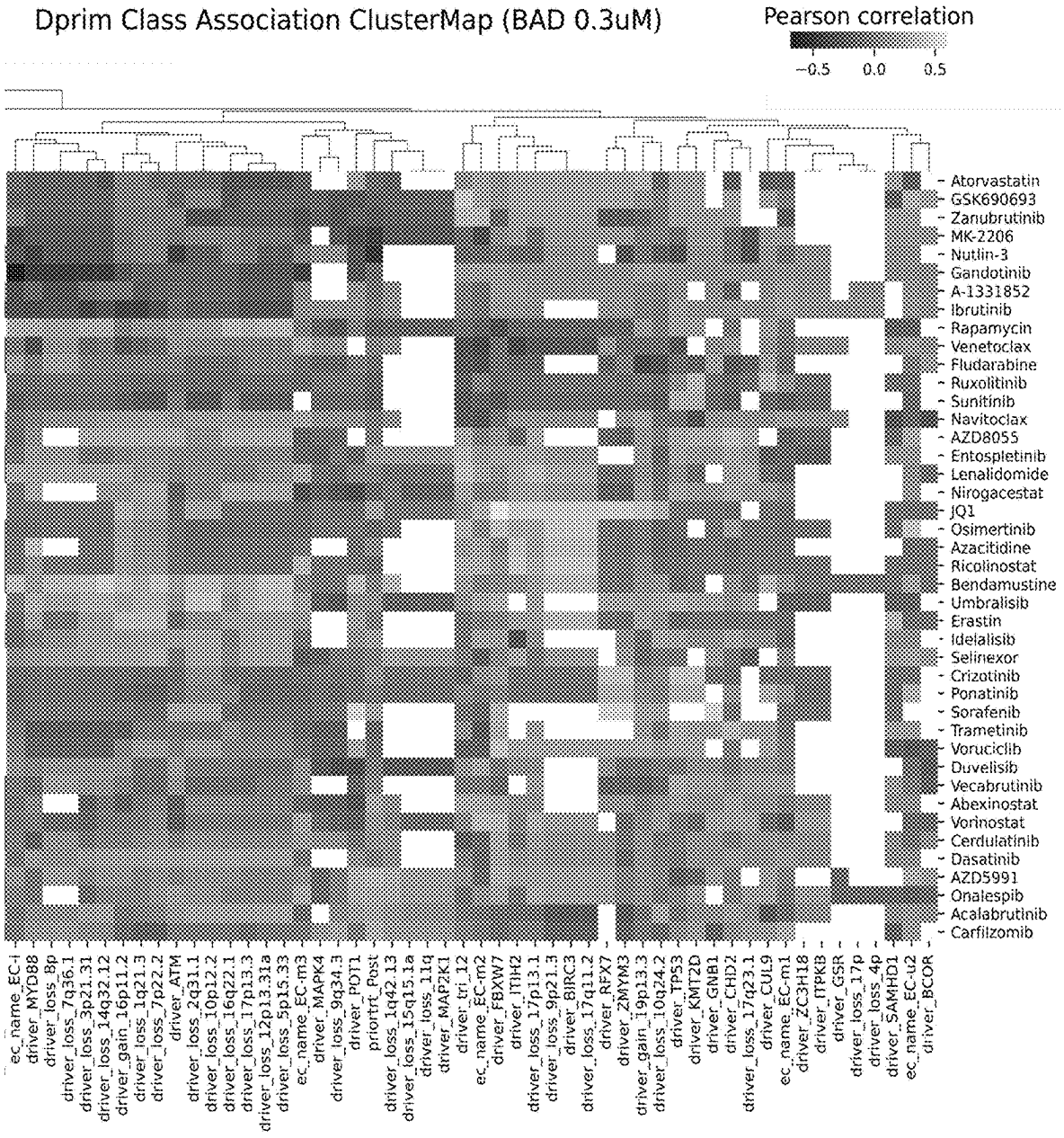


FIG. 31 (Continued)

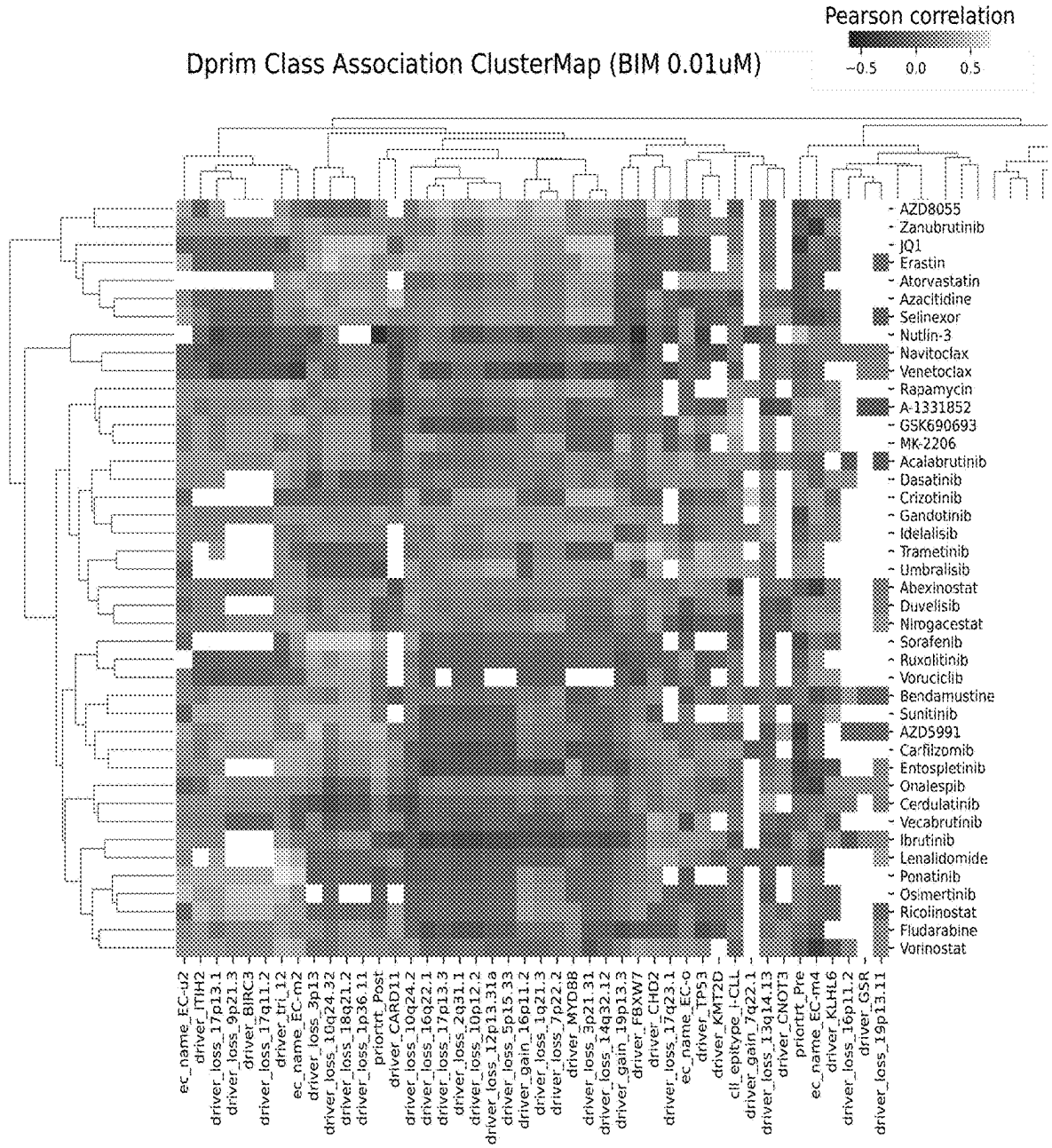

Dprim Class Association ClusterMap (BIM 0.01uM)
Pearson correlation
−0.5
0.0
0.5
AZD8055
Zanubrutinib
JQ1
Erastin
Atorvastatin
Azacitidine
Selinexor
Nutlin-3
Navitoclax
Venetoclax
Rapamycin
A-1331852
GSK690693
MK-2206
Acalabrutinib
Dasatinib
Crizotinib
Gandotinib
Idelalisib
Trametinib
Umbralisib
Abexinostat
Duvelisib
Nirogacestat
Sorafenib
Ruxolitinib
Voruciclib
Bendamustine
Sunitinib
AZD5991
Carfilzomib
Entospletinib
Onalespib
Cerdulatinib
Vecabrutinib
Ibrutinib
Lenalidomide
Ponatinib
Osimertinib
Ricolinostat
Fludarabine
Vorinostat
ec_name_EC-u2
driver_ITIH2
driver_loss_17p13.1
driver_loss_9p21.3
driver_BIRC3
driver_loss_17q11.2
driver_tri_12
ec_name_EC-m2
driver_loss_3p13
driver_loss_10q24.32
driver_loss_18q21.2
driver_loss_1p36.11
priortrt_Post
driver_CARD11
driver_loss_10q24.2
driver_loss_16q22.1
driver_loss_17p13.3
driver_loss_2q31.1
driver_loss_10p12.2
driver_loss_12p13.31a
driver_loss_5p15.33
driver_gain_16p11.2
driver_loss_1q21.3
driver_loss_7p22.2
driver_MYD88
driver_loss_3p21.31
driver_loss_14q32.12
driver_gain_19p13.3
driver_FBXW7
driver_CHD2
driver_loss_17q23.1
ec_name_EC-o
driver_TP53
driver_KMT2D
cll_epitype_i-CLL
driver_gain_7q22.1
driver_loss_13q14.13
driver_CNOT3
priortrt_Pre
ec_name_EC-m4
driver_KLHL6
driver_loss_16p11.2
driver_GSR
driver_loss_19p13.11

FIG. 32

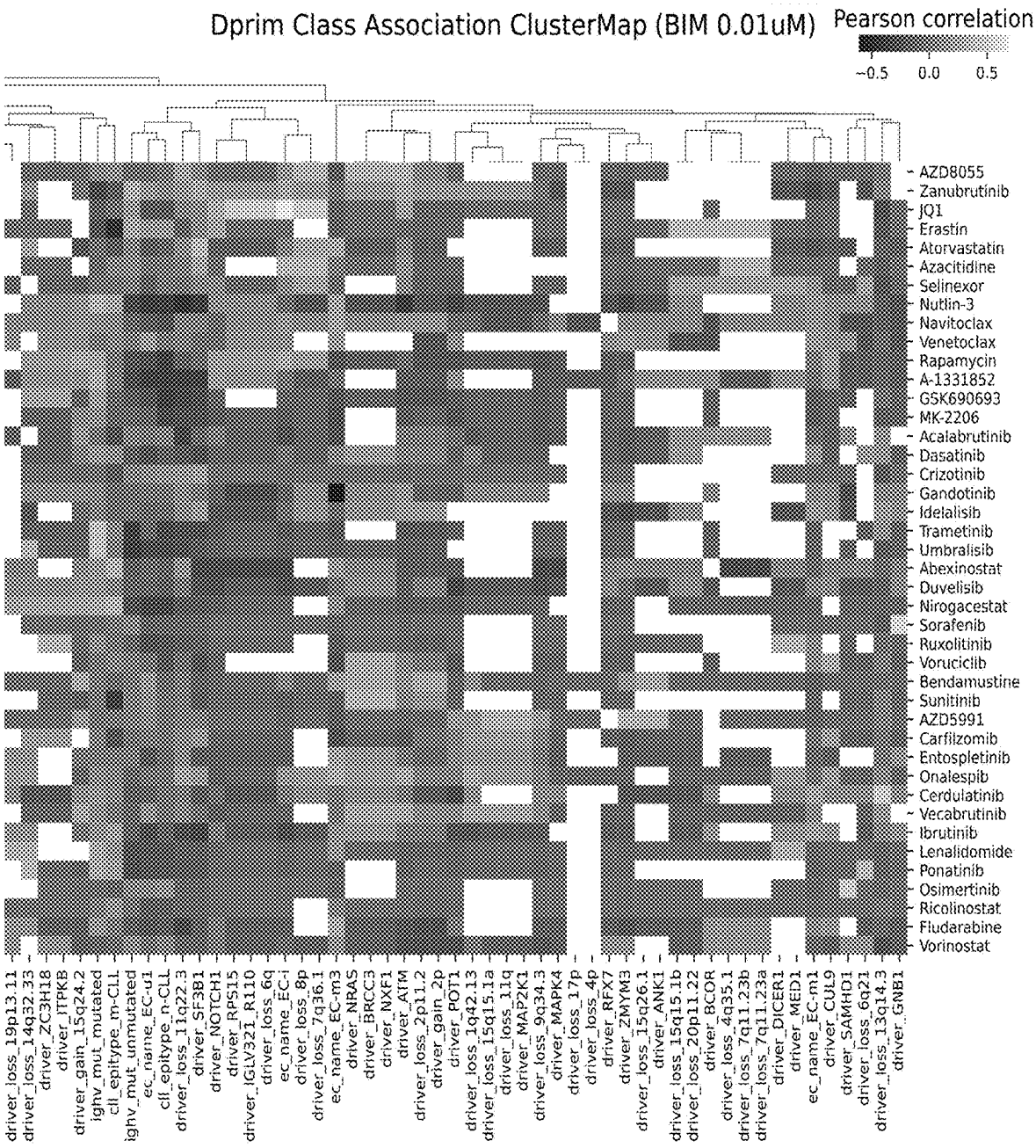


FIG. 32 (Continued)

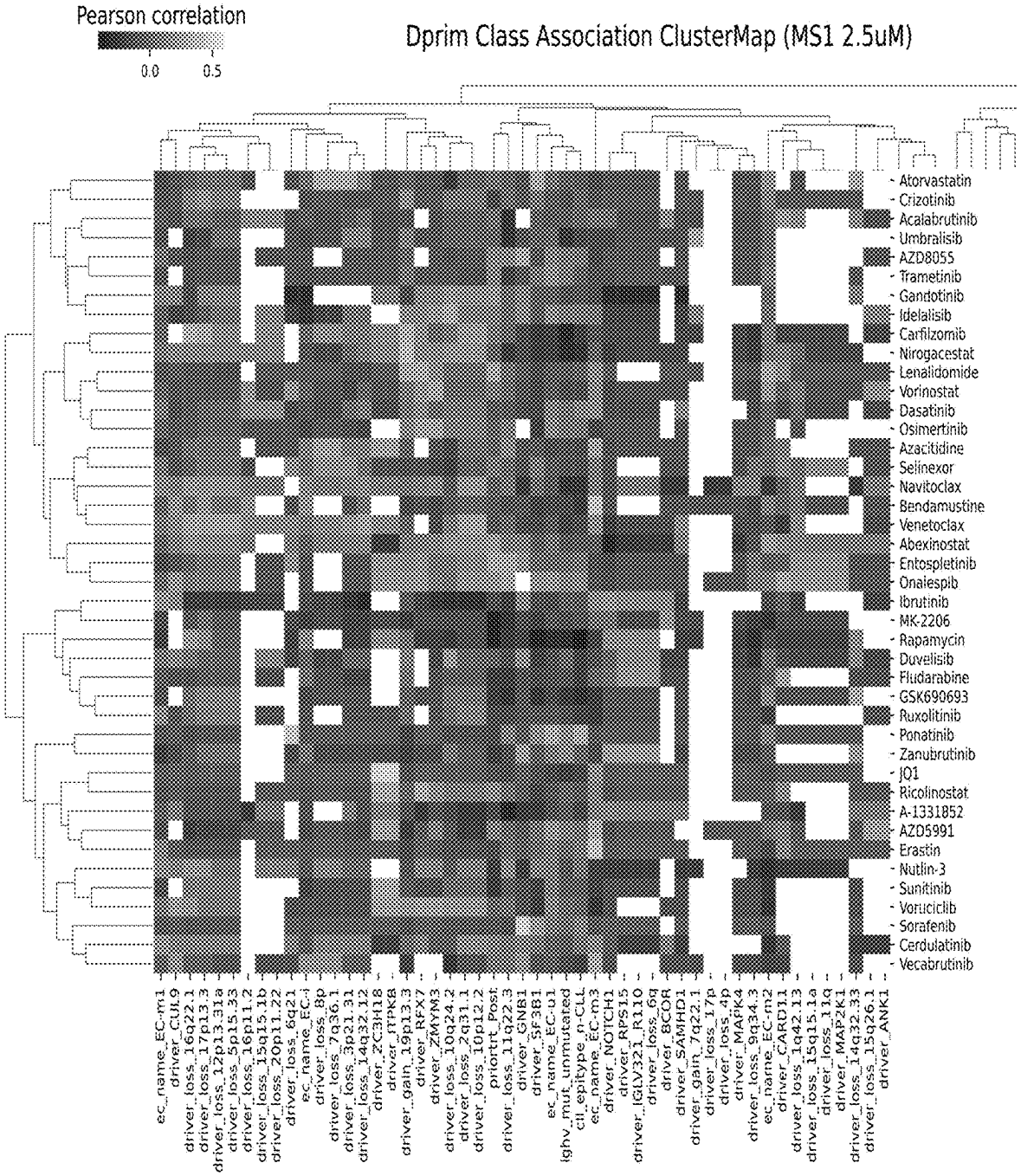

Pearson correlation
0.0
0.5
Dprim Class Association ClusterMap (MS1 2.5uM)
Atorvastatin
Crizotinib
Acalabrutinib
Umbralisib
AZD8055
Trametinib
Gandotinib
Idelalisib
Carfilzomib
Nirogacestat
Lenalidomide
Vorinostat
Dasatinib
Osimertinib
Azacitidine
Selinexor
Navitoclax
Bendamustine
Venetoclax
Abexinostat
Entospletinib
Onalespib
Ibrutinib
MK-2206
Rapamycin
Duvelisib
Fludarabine
GSK690693
Ruxolitinib
Ponatinib
Zanubrutinib
JQ1
Ricolinostat
A-1331852
AZD5991
Erastin
Nutlin-3
Sunitinib
Voruciclib
Sorafenib
Cerdulatinib
Vecabrutinib
ec_name_EC-m1
driver_CUL9
driver_loss_16q22.1
driver_loss_17p13.3
driver_loss_12p13.31a
driver_loss_5p15.33
driver_loss_16p11.2
driver_loss_15q15.1b
driver_loss_20p11.22
driver_loss_6q21
ec_name_EC-i
driver_loss_8p
driver_loss_7q36.1
driver_loss_3p21.31
driver_loss_14q32.12
driver_ZC3H18
driver_TTPK8
driver_gain_19p13.3
driver_RFX7
driver_ZMYM3
driver_loss_10q24.2
driver_loss_2q31.1
driver_loss_10p12.2
priortrt_Post
driver_loss_11q22.3
driver_GNB1
driver_SF3B1
ec_name_EC-u1
ighv_mut_unmutated
cll_epitype_n-CLL
ec_name_EC-m3
driver_NOTCH1
driver_RPS15
driver_IGLV321_R110
driver_loss_6q
driver_BCOR
driver_SAMHD1
driver_gain_7q22.1
driver_loss_17p
driver_loss_4p
driver_MAPK4
driver_loss_9q34.3
ec_name_EC-m2
driver_CARD11
driver_loss_1q42.13
driver_loss_15q15.1a
driver_loss_11q
driver_MAP2K1
driver_loss_14q32.33
driver_loss_15q26.1
driver_ANK1

FIG. 33

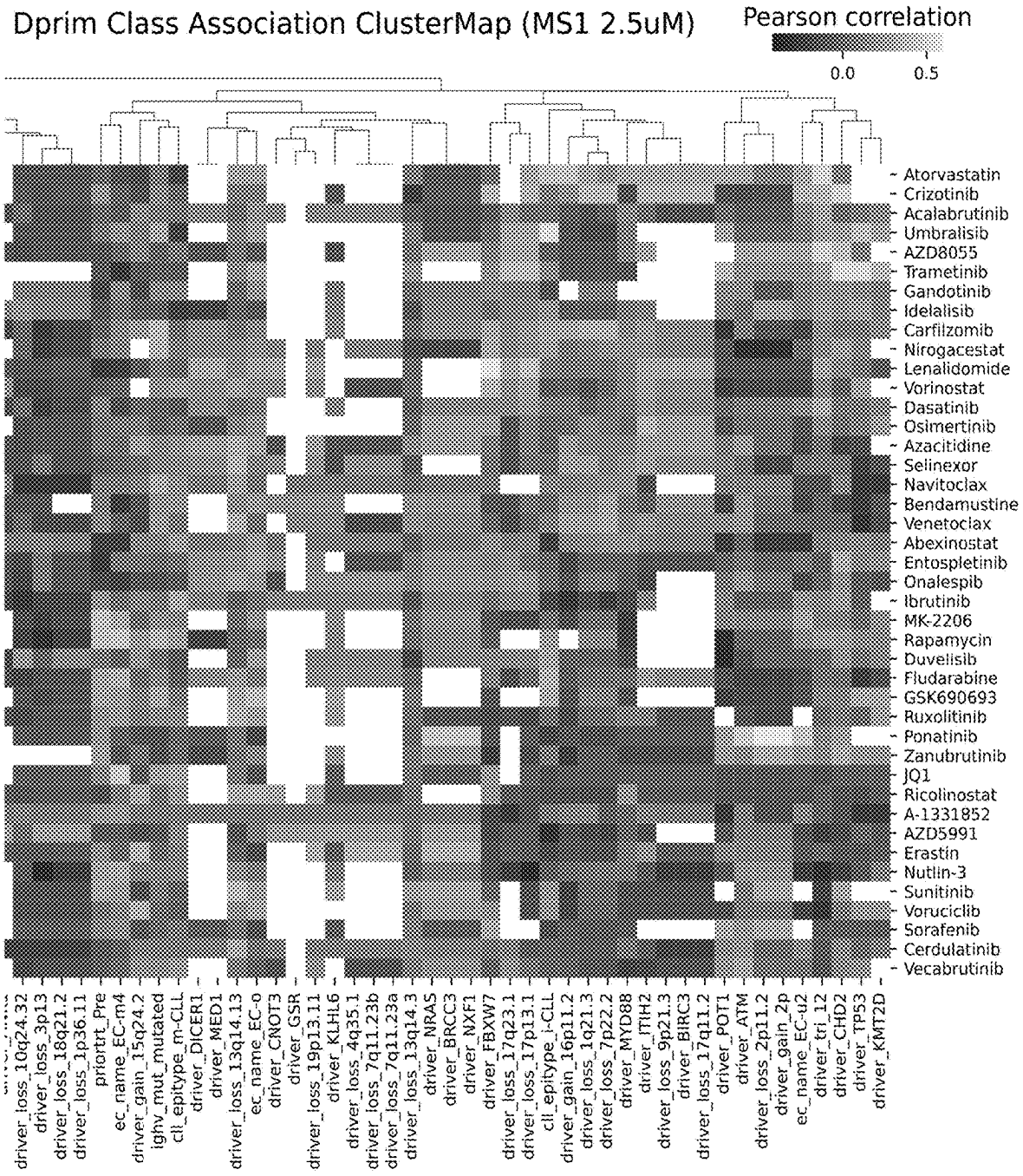


FIG. 33 (Continued)

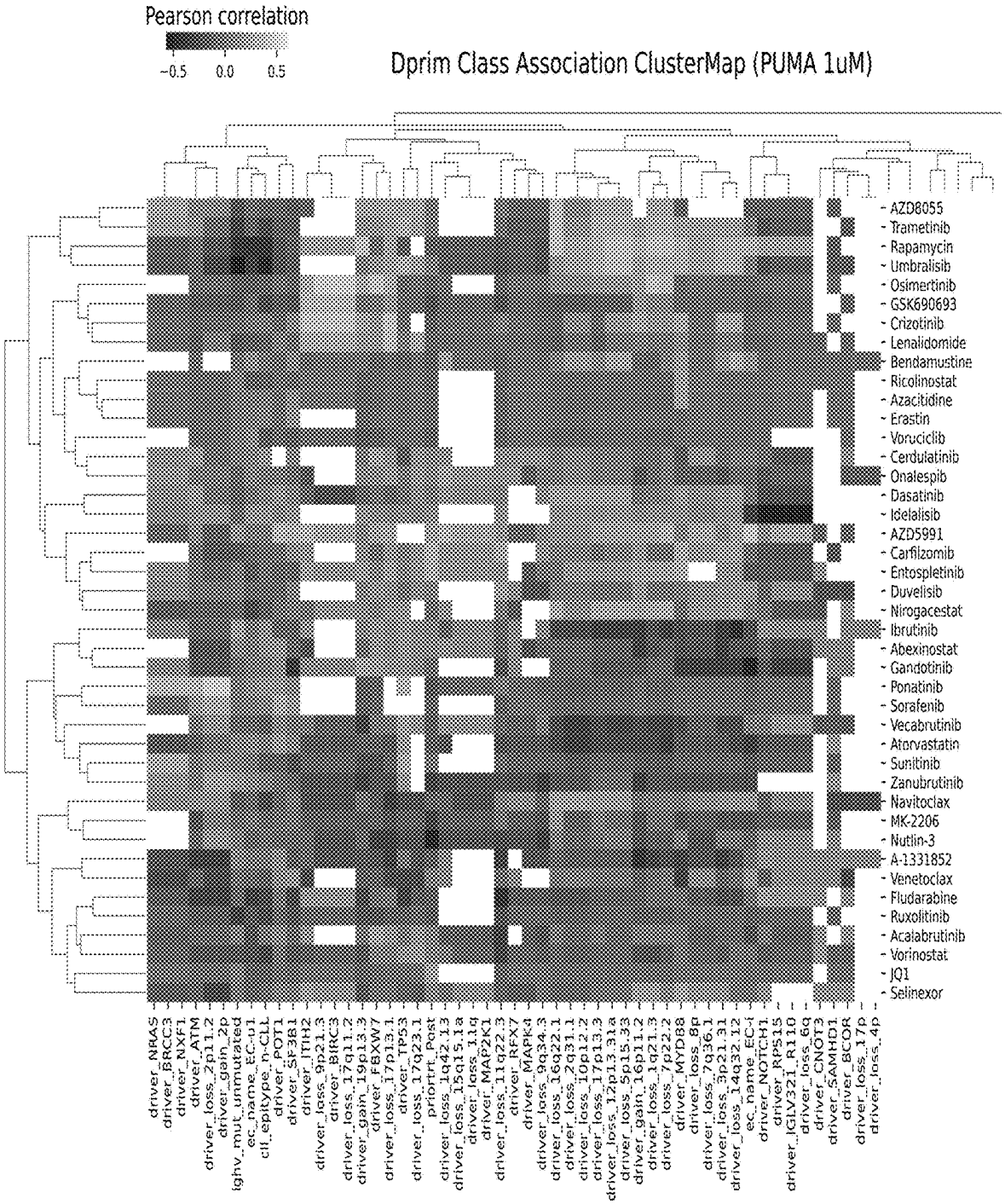

Pearson correlation
−0.5
0.0
0.5
Dprim Class Association ClusterMap (PUMA 1uM)
AZD8055
Trametinib
Rapamycin
Umbralisib
Osimertinib
GSK690693
Crizotinib
Lenalidomide
Bendamustine
Ricolinostat
Azacitidine
Erastin
Voruciclib
Cerdulatinib
Onalespib
Dasatinib
Idelalisib
AZD5991
Carfilzomib
Entospletinib
Duvelisib
Nirogacestat
Ibrutinib
Abexinostat
Gandotinib
Ponatinib
Sorafenib
Vecabrutinib
Atorvastatin
Sunitinib
Zanubrutinib
Navitoclax
MK-2206
Nutlin-3
A-1331852
Venetoclax
Fludarabine
Ruxolitinib
Acalabrutinib
Vorinostat
JQ1
Selinexor
driver_NRAS
driver_BRCC3
driver_NXF1
driver_ATM
driver_loss_2p11.2
driver_gain_2p
ighv_mut_unmutated
ec_name_EC-u1
cll_epitype_n-CLL
driver_POT1
driver_SF3B1
driver_ITIH2
driver_loss_9p21.3
driver_BIRC3
driver_loss_17q11.2
driver_gain_19p13.3
driver_FBXW7
driver_loss_17p13.1
driver_TP53
driver_loss_17q23.1
priortrt_Post
driver_loss_1q42.13
driver_loss_15q15.1a
driver_loss_11q
driver_MAP2K1
driver_loss_11q22.3
driver_RFX7
driver_MAPK4
driver_loss_9q34.3
driver_loss_16q22.1
driver_loss_2q31.1
driver_loss_10p12.2
driver_loss_17p13.3
driver_loss_12p13.31a
driver_loss_5p15.33
driver_gain_16p11.2
driver_loss_1q21.3
driver_loss_7p22.2
driver_MYD88
driver_loss_8p
driver_loss_7q36.1
driver_loss_3p21.31
driver_loss_14q32.12
ec_name_EC-i
driver_NOTCH1
driver_RP515
driver_IGLV321_R110
driver_loss_6q
driver_CNOT3
driver_SAMHD1
driver_BCOR
driver_loss_17p
driver_loss_4p

FIG. 34

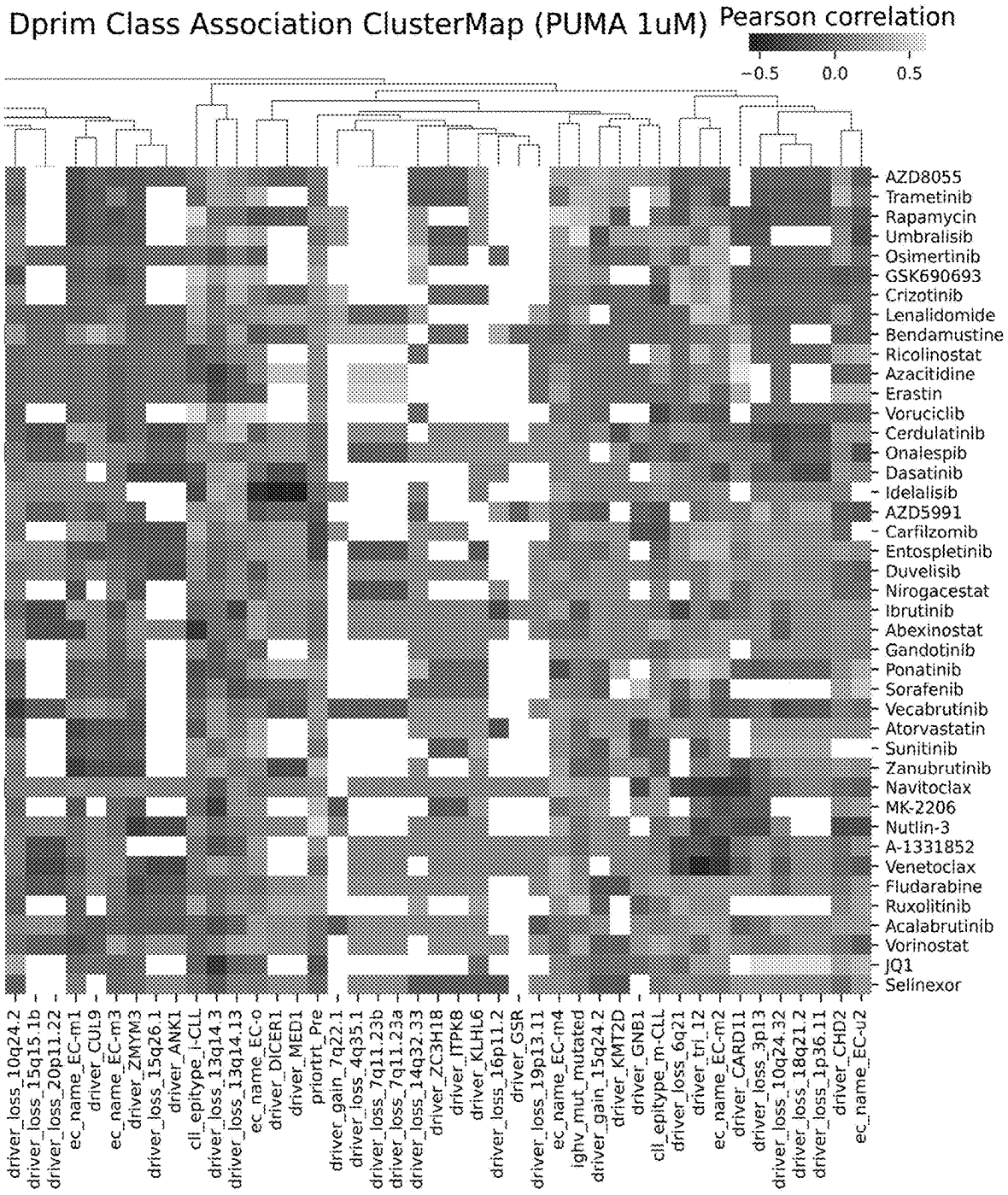


FIG. 34 (Continued)

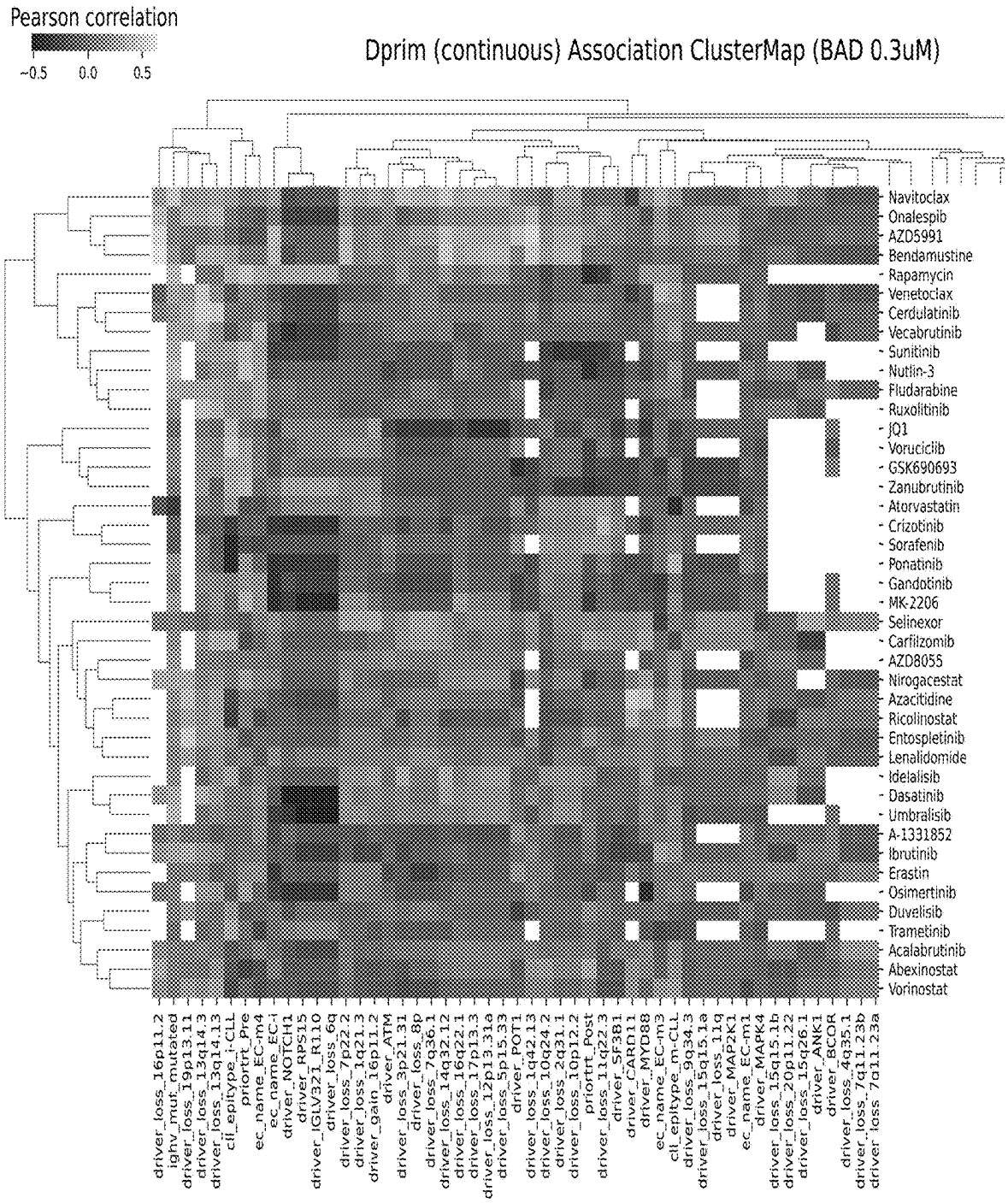

Pearson correlation
-0.5
0.0
0.5
Dprim (continuous) Association ClusterMap (BAD 0.3uM)
Navitoclax
Onalespib
AZD5991
Bendamustine
Rapamycin
Venetoclax
Cerdulatinib
Vecabrutinib
Sunitinib
Nutlin-3
Fludarabine
Ruxolitinib
JQ1
Voruciclib
GSK690693
Zanubrutinib
Atorvastatin
Crizotinib
Sorafenib
Ponatinib
Gandotinib
MK-2206
Selinexor
Carfilzomib
AZD8055
Nirogacestat
Azacitidine
Ricolinostat
Entospletinib
Lenalidomide
Idelalisib
Dasatinib
Umbralisib
A-1331852
Ibrutinib
Erastin
Osimertinib
Duvelisib
Trametinib
Acalabrutinib
Abexinostat
Vorinostat
driver_loss_16p11.2
igh_mut_mutated
driver_loss_19p13.11
driver_loss_13q14.3
driver_loss_13q14.13
cll_epitype_i-CLL
priortrt_Pre
ec_name_EC-m4
ec_name_EC-i
driver_NOTCH1
driver_RPS15
driver_IGLV321_R110
driver_loss_6q
driver_loss_7p22.2
driver_loss_1q21.3
driver_gain_16p11.2
driver_ATM
driver_loss_3p21.31
driver_loss_8p
driver_loss_7q36.1
driver_loss_14q32.12
driver_loss_16q22.1
driver_loss_17p13.3
driver_loss_12p13.31a
driver_loss_5p15.33
driver_POT1
driver_loss_1q42.13
driver_loss_10q24.2
driver_loss_2q31.1
driver_loss_10p12.2
priortrt_Post
driver_loss_11q22.3
driver_SF3B1
driver_CARD11
driver_MYD88
ec_name_EC-m3
cll_epitype_m-CLL
driver_loss_9q34.3
driver_loss_15q15.1a
driver_loss_11q
driver_MAP2K1
ec_name_EC-m1
driver_MAPK4
driver_loss_15q15.1b
driver_loss_20p11.22
driver_loss_15q26.1
driver_ANK1
driver_BCOR
driver_loss_4q35.1
driver_loss_7q11.23b
driver_loss_7q11.23a

FIG. 35

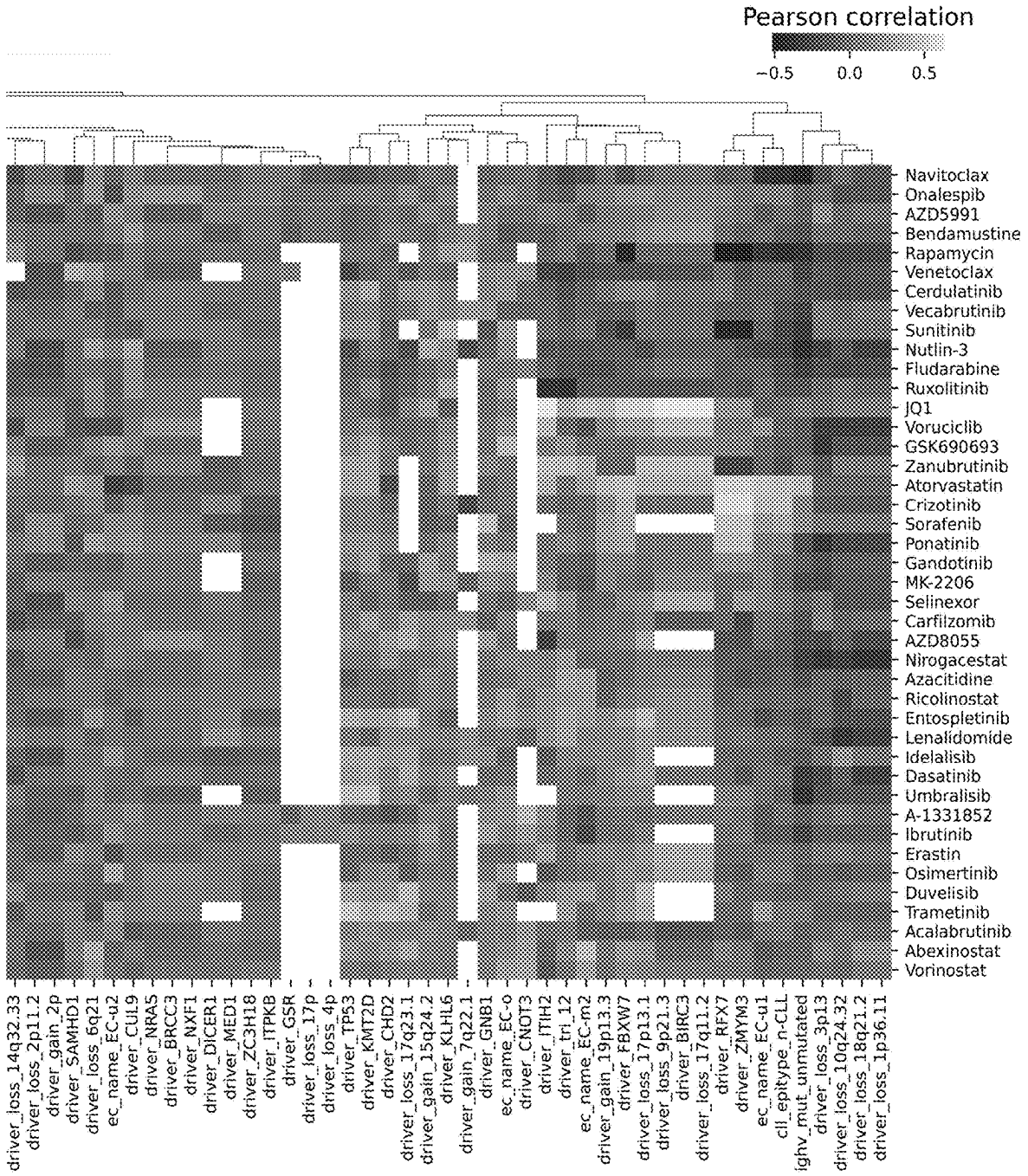


FIG.35 (Continued)

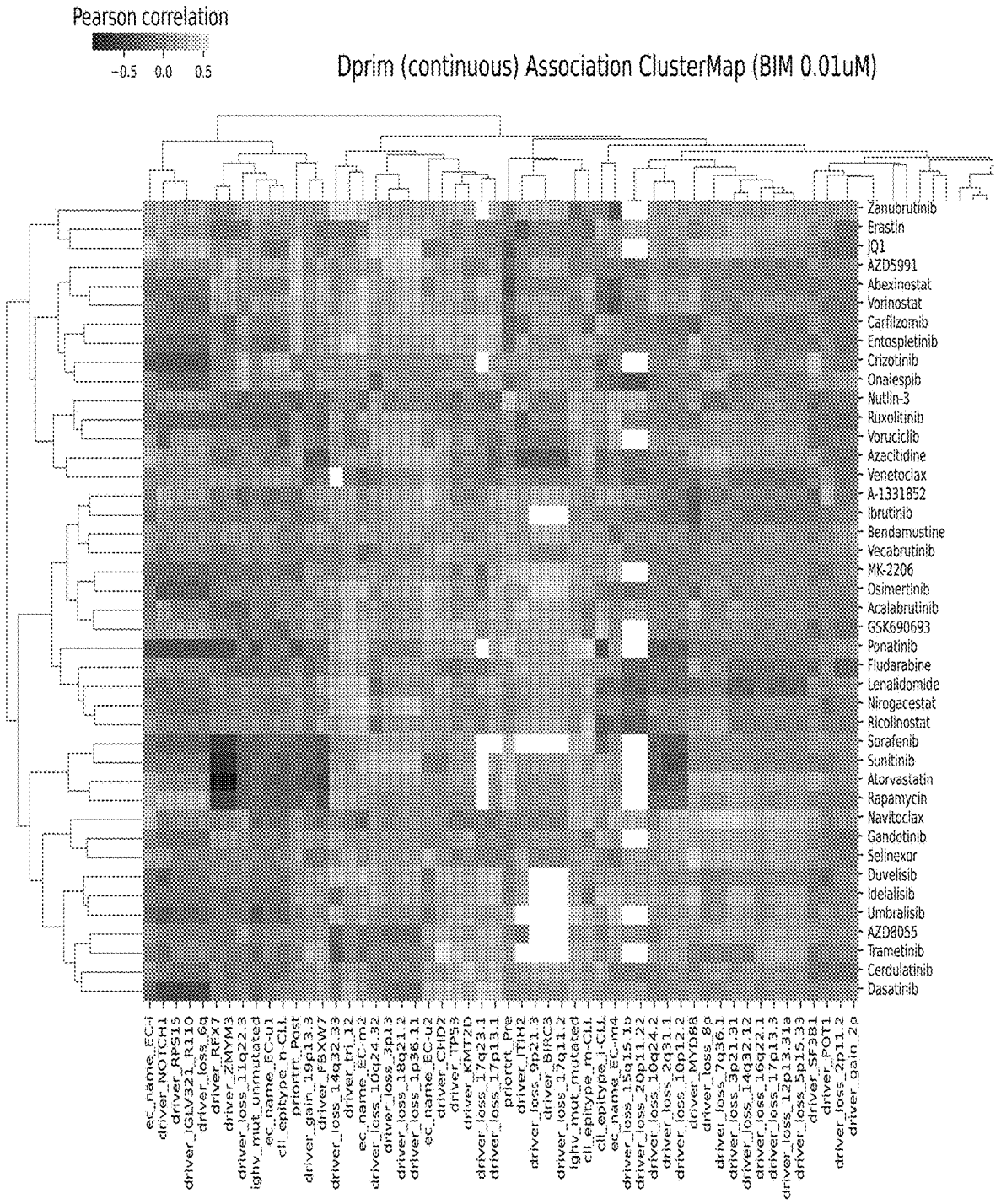

Pearson correlation
-0.5 0.0 0.5
Dprim (continuous) Association ClusterMap (BIM 0.01uM)
Zanubrutinib
Erastin
JQ1
AZD5991
Abexinostat
Vorinostat
Carfilzomib
Entospletinib
Crizotinib
Onalespib
Nutlin-3
Ruxolitinib
Voruciclib
Azacitidine
Venetoclax
A-1331852
Ibrutinib
Bendamustine
Vecabrutinib
MK-2206
Osimertinib
Acalabrutinib
GSK690693
Ponatinib
Fludarabine
Lenalidomide
Nirogacestat
Ricolinostat
Sorafenib
Sunitinib
Atorvastatin
Rapamycin
Navitoclax
Gandotinib
Selinexor
Duvelisib
Idelalisib
Umbralisib
AZD8055
Trametinib
Cerdulatinib
Dasatinib
ec_name_EC-i
driver_NOTCH1
driver_RPS15
driver_IGLV321_R110
driver_loss_6q
driver_RFX7
driver_ZMYM3
driver_loss_11q22.3
ighv_mut_unmutated
ec_name_EC-u1
cll_epitype_n-CLL
priortrt_Post
driver_gain_19p13.3
driver_FBXW7
driver_loss_14q32.33
driver_tri_12
ec_name_EC-m2
driver_loss_10q24.32
driver_loss_3p13
driver_loss_18q21.2
driver_loss_1p36.11
ec_name_EC-u2
driver_CHD2
driver_TP53
driver_KMT2D
driver_loss_17q23.1
driver_loss_17p13.1
priortrt_Pre
driver_ITH2
driver_loss_9p21.3
driver_BIRC3
driver_loss_17q11.2
ighv_mut_mutated
cll_epitype_m-CLL
cll_epitype_i-CLL
ec_name_EC-m4
driver_loss_15q15.1b
driver_loss_20p11.22
driver_loss_10q24.2
driver_loss_2q31.1
driver_loss_10p12.2
driver_MYD88
driver_loss_8p
driver_loss_7q36.1
driver_loss_3p21.31
driver_loss_14q32.12
driver_loss_16q22.1
driver_loss_17p13.3
driver_loss_12p13.31a
driver_loss_5p15.33
driver_SF3B1
driver_POT1
driver_loss_2p11.2
driver_gain_2p

FIG. 36

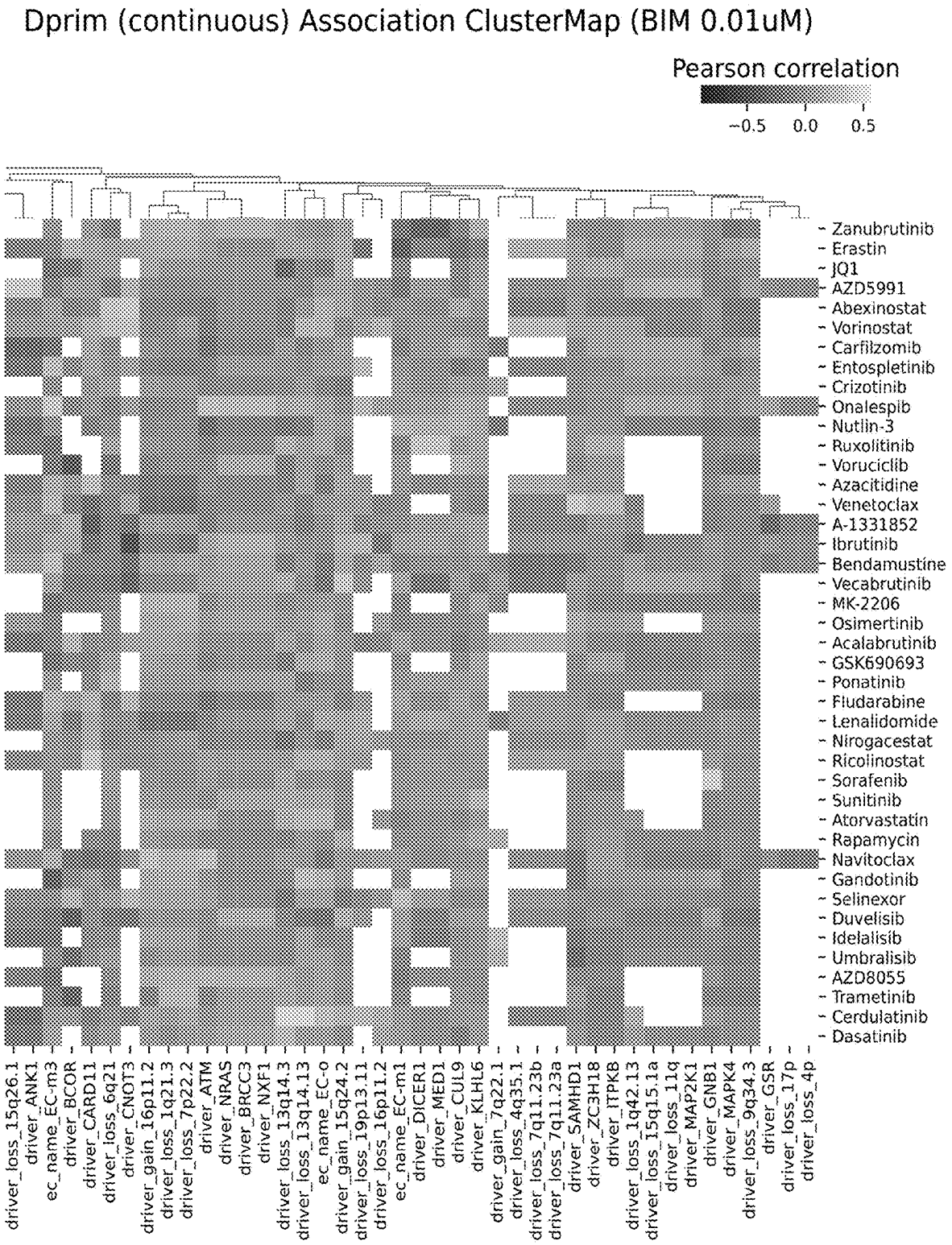


FIG. 36 (Continued)

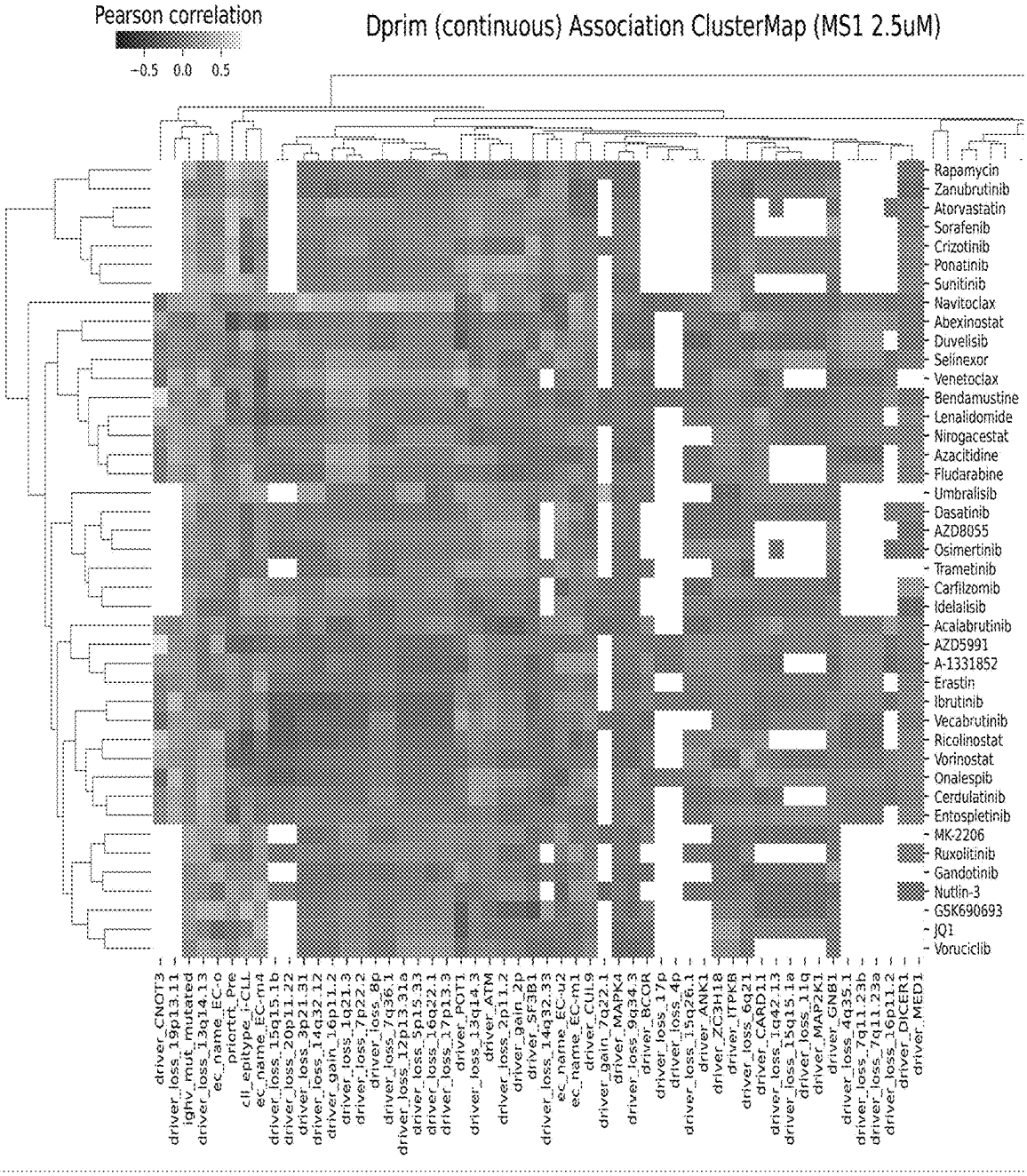

Pearson correlation
-0.5 0.0 0.5
Dprim (continuous) Association ClusterMap (MS1 2.5uM)
driver_CNOT3
driver_loss_19p13.11
igHv_mut_mutated
driver_loss_13q14.13
ec_name_EC-o
priortrt_Pre
cll_epitype_i-CLL
ec_name_EC-m4
driver_loss_15q15.1b
driver_loss_20p11.22
driver_loss_3p21.31
driver_loss_14q32.12
driver_gain_16p11.2
driver_loss_1q21.3
driver_loss_7p22.2
driver_loss_8p
driver_loss_7q36.1
driver_loss_12p13.31a
driver_loss_5p15.33
driver_loss_16q22.1
driver_loss_17p13.3
driver_POT1
driver_loss_13q14.3
driver_ATM
driver_loss_2p11.2
driver_gain_2p
driver_SF3B1
driver_loss_14q32.33
ec_name_EC-u2
ec_name_EC-m1
driver_CUL9
driver_gain_7q22.1
driver_MAPK4
driver_loss_9q34.3
driver_BCOR
driver_loss_17p
driver_loss_4p
driver_loss_15q26.1
driver_ANK1
driver_ZC3H18
driver_ITPKB
driver_loss_6q21
driver_CARD11
driver_loss_1q42.13
driver_loss_15q15.1a
driver_loss_11q
driver_MAP2K1
driver_GNB1
driver_loss_4q35.1
driver_loss_7q11.23b
driver_loss_7q11.23a
driver_loss_16p11.2
driver_DICER1
driver_MED1
Rapamycin
Zanubrutinib
Atorvastatin
Sorafenib
Crizotinib
Ponatinib
Sunitinib
Navitoclax
Abexinostat
Duvelisib
Selinexor
Venetoclax
Bendamustine
Lenalidomide
Nirogacestat
Azacitidine
Fludarabine
Umbralisib
Dasatinib
AZD8055
Osimertinib
Trametinib
Carfilzomib
Idelalisib
Acalabrutinib
AZD5991
A-1331852
Erastin
Ibrutinib
Vecabrutinib
Ricolinostat
Vorinostat
Onalespib
Cerdulatinib
Entospletinib
MK-2206
Ruxolitinib
Gandotinib
Nutlin-3
GSK690693
JQ1
Voruciclib

FIG. 37

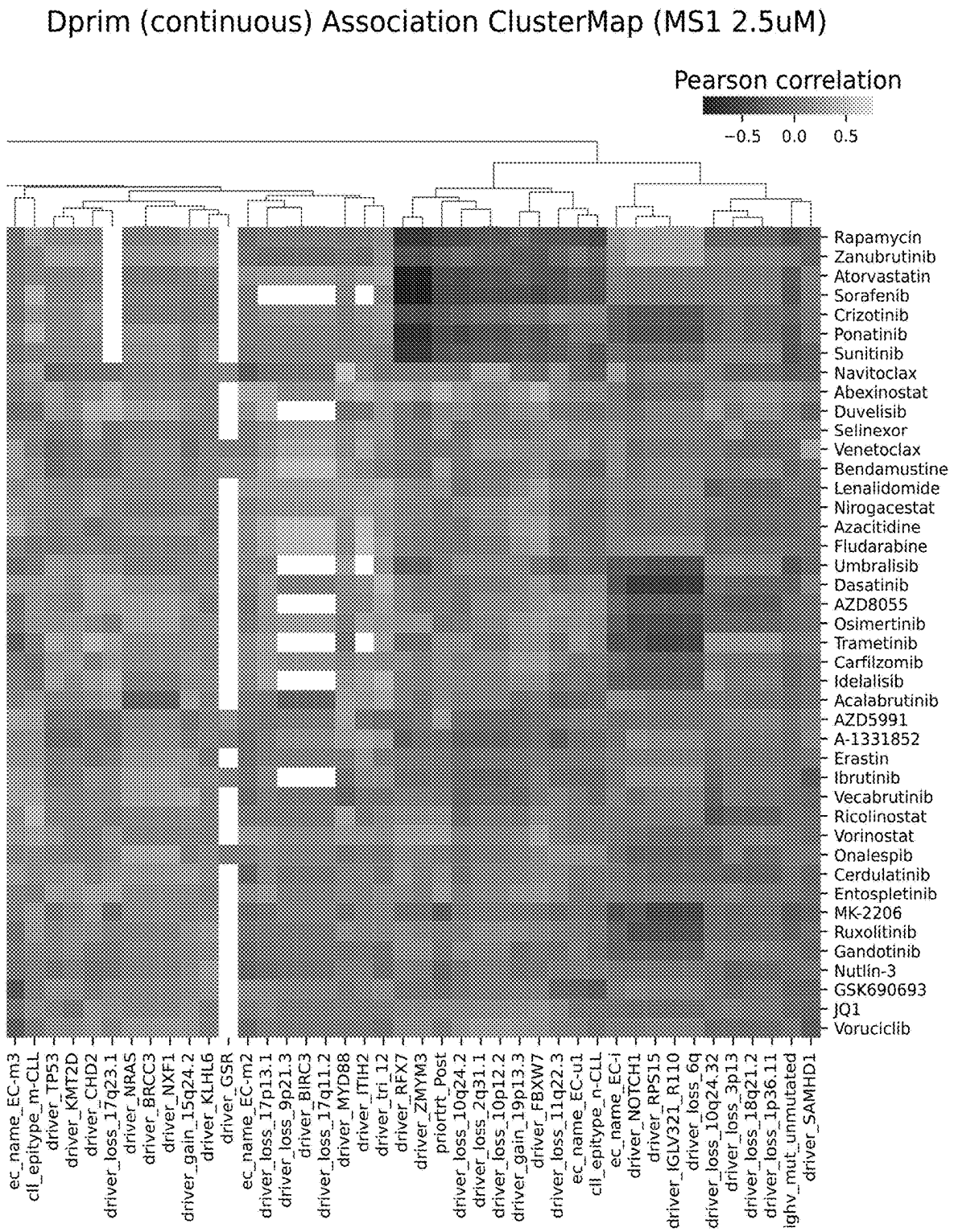


FIG. 37 (Continued)

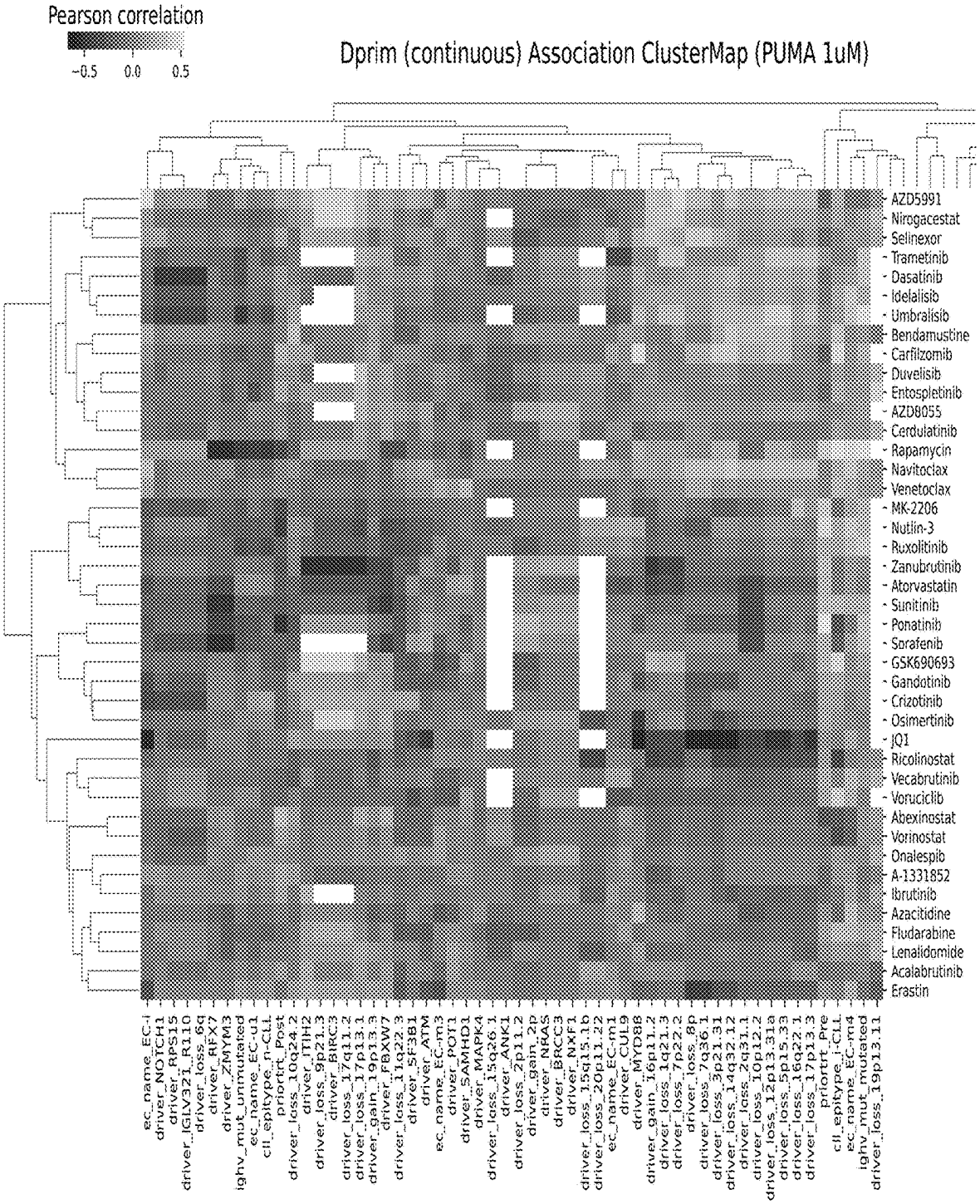

Pearson correlation
-0.5
0.0
0.5
Dprim (continuous) Association ClusterMap (PUMA 1uM)
AZD5991
Nirogacestat
Selinexor
Trametinib
Dasatinib
Idelalisib
Umbralisib
Bendamustine
Carfilzomib
Duvelisib
Entospletinib
AZD8055
Cerdulatinib
Rapamycin
Navitoclax
Venetoclax
MK-2206
Nutlin-3
Ruxolitinib
Zanubrutinib
Atorvastatin
Sunitinib
Ponatinib
Sorafenib
GSK690693
Gandotinib
Crizotinib
Osimertinib
JQ1
Ricolinostat
Vecabrutinib
Voruciclib
Abexinostat
Vorinostat
Onalespib
A-1331852
Ibrutinib
Azacitidine
Fludarabine
Lenalidomide
Acalabrutinib
Erastin
ec_name_EC-i
driver_NOTCH1
driver_RPS15
driver_IGLV321_R110
driver_loss_6q
driver_RFX7
driver_ZMYM3
ighv_mut_unmutated
ec_name_EC-u1
cll_epitype_n-CLL
priortrt_Post
driver_loss_10q24.2
driver_ITIH2
driver_loss_9p21.3
driver_BIRC3
driver_loss_17q11.2
driver_loss_17p13.1
driver_gain_19p13.3
driver_FBXW7
driver_loss_11q22.3
driver_SF3B1
driver_ATM
ec_name_EC-m3
driver_POT1
driver_SAMHD1
driver_MAPK4
driver_loss_15q26.1
driver_ANK1
driver_loss_2p11.2
driver_gain_2p
driver_NRAS
driver_BRCC3
driver_NXF1
driver_loss_15q15.1b
driver_loss_20p11.22
ec_name_EC-m1
driver_CUL9
driver_MYD88
driver_gain_16p11.2
driver_loss_1q21.3
driver_loss_7p22.2
driver_loss_8p
driver_loss_7q36.1
driver_loss_3p21.31
driver_loss_14q32.12
driver_loss_2q31.1
driver_loss_10p12.2
driver_loss_12p13.31a
driver_loss_5p15.33
driver_loss_16q22.1
driver_loss_17p13.3
priortrt_Pre
cll_epitype_i-CLL
ec_name_EC-m4
ighv_mut_mutated
driver_loss_19p13.11

FIG. 38

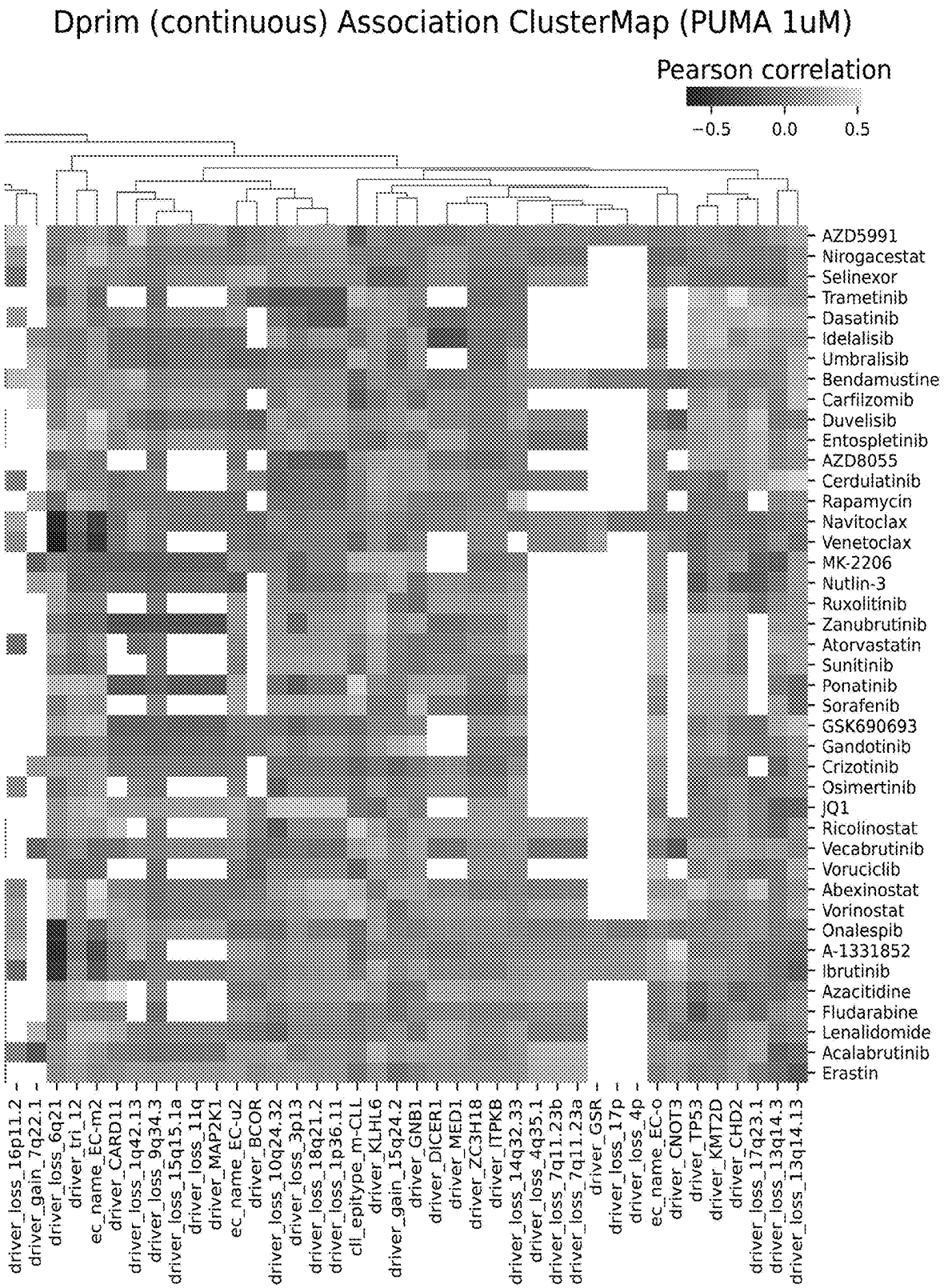


FIG. 38 (Continued)

drug_name*	normals**	M-CLL	U-CLL	i-CLL	m-CLL	n-CLL	EC-i	EC-m1	EC-m2	EC-m3	EC-m4	EC-o	EC-u1	EC-u2
A-1331852	-6.121	11.892	11.908	12.834	11.678	11.908	8.163	10.439	8.778	12.843	13.64	13.496	8.904	20.138
AZD5991	0.331	4.157	5.486	3.686	3.995	5.502	3.072	0.845	5.762	4.767	3.984	5.454	5.289	7.364
AZD8055	-2.629	3.827	3.552	2.465	4.429	6.211	4.247	1.718	2.47	1.229	3.813	5.104	4.941	8.329
Abexinostat	3.559	19.374	16.598	9.577	20.399	16.043	8.544	17.78	43.262	24.255	12.858	26.336	14.285	13.773
Acalabrutinib	2.966	8.652	9.263	9.902	8.32	9.263	3.981	3.24	12.829	3.692	7.728	10.809	8.57	13.349
Azacitidine	-6.202	2.152	1.269	0.861	2.805	0.432	1.906	1.751	3.845	2.763	2.757	2.708	-1.139	2.115
Bendamustin	-3.27	2.615	3.264	4.13	2.147	1.959	8.51	-0.619	5.064	4.657	1.08	1.462	2.01	7.601
Carfilzomib	-13.865	8.689	5.183	10.782	7.474	6.773	4.231	11.241	14.484	3.485	8.256	7.61	5.183	18.871
Cerdulatinib	-6.598	14.444	11.29	18.509	13.991	13.503	15.967	16.913	4.83	13.813	13.959	23.712	10.886	15.039
Dasatinib	-5.002	10.851	11.445	10.999	10.851	14.726	6.995	9.974	8.513	13.387	9.51	11.415	11.206	19.779
Duvelisib	-1.655	12.376	10.231	12.833	12.032	9.396	9.5	14.945	23.755	11.556	11.635	11.272	9.716	10.794
Entospletinib	-7.957	8.195	8.176	8.331	8.195	8.176	5.216	-0.032	19.676	7.29	7.879	17.024	5.982	12.962
Erastin	0.483	2.491	2.234	2.872	2.408	1.825	1.875	3.225	2.799	0.178	3.214	2.414	1.958	0.309
Fludarabine	-7.54	9.622	3.936	11.085	8.965	2.243	6.372	5.786	9.624	9.558	10.937	7.322	2.243	7.5
GSK690693	-1.552	5.535	2.303	10.101	4.061	1.938	2.177	1.891	10.013	-1.799	6.768	12.232	1.938	7.046
Gandotinib	2.471	17.845	12.768	18.495	16.873	12.768	-5.218	13.876	14.153	5.772	20.261	29.895	14.567	8.548
Ibrutinib	-6.942	11.977	12.962	9.855	12.747	12.72	3.148	12.393	8.828	15.365	11.407	15.777	8.733	22.96
Idelalisib	0.86	12.042	11.931	19.34	10.61	11.395	3.915	8.282	15.039	8.198	16.885	9.661	11.288	15.952
JQ1	-1.76	1.149	1.828	2.94	0.976	1.527	-3.559	-1.2	4.389	-0.992	2.323	-0.49	-0.113	3.595
Lenalidomide	-8.719	2.559	1.128	4.547	2.187	1.109	3.101	-1.24	11.65	3.852	0.728	4.784	0.396	4.552
MK-2206	-3.669	7.384	3.692	7.378	7.98	3.692	-4.684	5.371	4.982	2.173	8.838	9.192	5.546	10.009
Navitoclax	-3.245	18.724	10.17	20.414	18.201	7.642	36.529	20.92	4.532	24.275	26.071	13.379	9.473	17.15
Nirogacestat	-8.717	9.01	4.931	7.651	9.306	4.931	7.52	5.813	12.164	6.845	9.07	7.5	3.85	8.632
Nutlin-3	-11.098	18.813	11.044	19.847	15.905	12.981	7.181	31.071	6.231	12.423	25.3	16.231	11.044	37.328
Onalespib	-4.38	5.939	5.772	5.49	5.976	12.206	5.847	0.114	7.648	12.71	2.762	10.637	7.061	-1.158
Osimertinib	-4.553	1.176	0.722	0.87	1.621	1.215	-5.247	-0.272	-0.371	-0.498	0.559	3.885	1.214	2.552
Ricolinostat	1.942	-1.124	-4.548	-7.994	0.578	-4.548	-10.23	6.778	1.134	-0.11	-0.328	2.749	-6.54	4.054
Ruxolitinib	-8.991	3.752	0.91	2.679	3.752	0.316	-1.75	5.128	0.132	0.505	7.912	3.9	-0.072	7.753
Selinexor	-5.346	7.142	5.193	7.411	6.673	5.066	8.235	10.963	5.194	4.288	6.715	7.155	5.066	14.755
Trametinib	1.405	6.413	4.372	7.096	6.347	4.372	1.23	0.124	2.327	3.404	5.239	8.337	5.346	17.505
Umbralisib	2.325	7.773	3.786	12.319	5.69	3.864	-3.959	0.348	10.335	5.036	8.257	7.436	4.086	5.684
Vecabrutinib	-0.097	7.356	6.184	6.962	7.987	6.184	6.776	7.873	2.365	8.493	9.441	7.617	6.605	14.365
Venetoclax	4.838	15.091	8.574	14.804	14.939	8.574	15.93	12.492	1.476	27.262	14.947	15.357	8.574	21.606
Vorinostat	3.315	7.212	4.514	0.886	7.966	4.251	-5.863	-6.263	18.351	12.951	2.17	14.482	1.743	8.903
Voruciclib	-2.36	4.706	5.275	6.217	4.739	3.672	6.028	-1.396	0.909	1.225	7.667	8.119	5.06	4.37

*The 35 drugs tested on the normals are listed

**The Normals column is the median delta-priming value across all peptides, donors and sample types (CD19, CD3, CD14).

All other columns contain median delta-priming values for tumors associated

FIG. 39

age_above_60	Post_treatment	driver_ANK1	driver_ATM	driver_BCOR	driver_BIRC3	driver_BRCC3	driver_CARD11	driver_CHD2	driver_CNOT3	driver_CUL9	driver_DICER1
11.118	8.068	11.137	5.906	21.382	19.314	11.114	4.595	7.225	33.148	17.493	12.02
4.207	7.698	8.961	1.972	5.034	16.389	1.124	7.162	2.174	9.773	4.16	6.697
5.211	6.652	-2.224	8.643			18.131		12.655		3.425	1.28
20.197	40.2	12.23	6.706	7.159	10.588	11.786	17.013	21.029	16.888	32.243	14.4
10.665	10.533	-0.483	7.121	17.009	3.772	4.928	9.942	14.495	19.218	1.523	13.741
2.551	3.311	-6.493	-1.728	2.115	7.271	-0.545	14.178	0.896	4.681	0.429	9.085
3.383	2.81	-3.825	6.634	-4.628	19.771	9.592	1.992	4.037	-7.742	12.161	-2.646
7.412	11.5	-8.963	6.44		7.594	7.31	14.899	12.802		13.265	12.683
13.422	24.836	-8.275	23.172	13.503	13.719	26.241	4.403	13.497	10.168	16.913	20.262
11.728	8.102	-5.455	17.239		9.308	19.746	5.936	27.296		2.543	7.644
11.847	12.771	-2.205	10.308	-4.028		22.378	10.519	20.438	0.553	14.945	10.458
8.783	14.501	-5.05	8.788	7.231	13.669	12.96	15.067	17.251	18.086	2.589	19.293
2.863	2.933	0.733	1.712	4.17	6.215	1.712	7.446	2.194	7.355	-0.027	6.171
6.94	4.772	-3.991	1.485	15.54	26.032	3.833	13.734	6.679	17.183	18.757	11.49
3.47	0.018		1.938	6.063	14.875	4.218	-6.14	5.174		5.613	
13.231	12.626		12.452	13.328	21.788	16.721	8.194	14.738		24.46	
11.059	11.017	8.686	10.831	17.213		21.467	6.399	15.338	25.282	13.33	15.777
12.042	12.459	10.525	11.395			12.158	7.646	18.139		10.52	1.762
0.976	3.25		-1.23	-0.035	1.572	2.905	3.047	2.062		-0.597	
2.104	1.144	-6.452	-1.834	-8.374	17.259	0.889	4.141	10.527	-2.118	-0.204	15.774
6.667	0.626		5.546	8.636	14.824	11.283	-3.067	11.704		7.549	
13.883	10.253	19.327	39.177	-2.874	4.426	14.92	4.145	10.18	15.25	22.633	12.756
7.268	5.703		4.224	5.408	22.351	2.833	6.646	14.328	9.642	10.197	12.541
12.851	4.614	2.534	6.695		1.545	8.901	4.741	5.034		38.099	24.219
4.695	12.516	-1.388	28.415	-8.147	14.51	35.526	7.283	11.516	8.295	26.406	13.298
1.176	-2.921	-2.215	0.014		25.78	8.847		2.762		-2.554	2.668
-2.671	-4.066	-4.799	-3.764	-5.719	3.488	-1.516	16.339	-2.244	-1.506	-7.423	3.966
1.316	-0.285	-1.37	1.414		-4.582	2.165		2.321		6.996	9.551
5.694	8.076	10.357	6.141	20.702	29.928	6.141	12.568	7.909	19.794	4.649	13.041
5.47	4.423		6.093	0.222		10.166		21.36		7.781	
5.162	4.543		4.385	2.128		3.718	4.754	10.789		5.675	
7.921	7.921		8.984	-2.906	3.302	12.095	0.951	11.736	-5.214	15.5	3.279
10.096	12.791	0.726	13.859	1.664	4.643	6.968	-1.072	13.19	20.372	15.537	
6.246	13.701	10.505	-3.797	4.514	12.047	2.93	19.337	6.567	37.871	0.498	10.736
4.444	2.651		5.275	-1.494	-0.804	13.575		6.328		12.166	

FIG. 39 (Continued)

driver_FBXW7	driver_GNB1	driver_GSR	driver_ITIH2	driver_ITPKB	driver_KUHL6	driver_KMT2D	driver_MAP2K1	driver_MAPK4	driver_MED1	driver_MYD88	driver_NOTCH1	driver_NRAS	driver_NXF1
10.076	9.738	11.968	16.962	13.57	15.981	5.353		4.782	12.02	8.836	18.187	13.519	11.114
5.65	1.762	4.097	6.819	8.136	8.789	1.336	14.371	-0.741	6.697	1.53	3.71	7.364	1.124
7.37	12.607		-1.664	-0.519	9.731	11.191		-0.189	1.28	7.267	-3.876	15.129	18.131
31.852	26.876		12.041	9.023	20.603	31.153	10.806	-1.551	14.4	17.512	-3.006	35.988	11.786
7.819	14.369		25.31	7.304	16.617	11.01	6.727	3.064	13.741	15.312	9.789	4.741	4.928
0.452	-0.727		7.271	8.41	5.399	1.658		4.497	9.085	8.111	0.189	1.833	-0.545
1.442	3.374	-3.527	-0.93	2.502	8.279	-0.458	2.832	-0.619	-2.646	0.933	-3.595	10.259	9.592
7.392	0.634		11.1	10.51	8.445	25.243	14.899	6.085	12.683	11.644	-2.511	15.685	7.31
19.421	24.98		11.693	7.281	30.723	47.482		12.745	20.262	6.054	1.312	26.241	26.241
13.057	3.845		10.122	4.258	20.871	31.741	5.936	5.692	7.644	16.621	-4.985	19.548	19.746
12.771	23.215		14.148	9.725	16.449	25.344	3.693	0.929	10.458	10.398	-1.781	20.309	22.378
7.879	10.961		20.104	8.081	4.957	29.653	20.002	-1.197	19.293	14.481	1.528	13.429	12.96
1.363	0.36		6.393	4.841	2.471	2.345	7.446	3.75	6.171	3.707	3.113	-1.602	1.712
4.97	7.601		26.032	7.384	12.692	3.991		-2.285	11.49	9.736	12.858	1.14	3.833
5.072	6.291		14.875	7.186	14.027	14.759	-6.14	0.093		1.085	5.011	5.848	4.218
17.887	40.328		21.788	16.399	25.818	30.69	8.194	6.249		2.358	1.857	8.618	16.721
13.103	20.273	19.395	21.379	9.69	18.995	16.27	7.757	7.914	15.777	1.773	14.657	25.372	21.467
14.013	17.586		17.449	6.475	18.691	31.312	7.646	7.278	1.762	22.889	-4.516	12.554	12.158
3.899	-0.179		1.572	7.818	-0.605	-0.775	3.047	-1.564		-7.493	-0.035	4.355	2.905
11.508	-0.572		17.259	5.781	6.722	-2.974	-1.209	-3.565	15.774	-2.118	-6.851	4.693	0.889
1.598	11.662		14.824	2.473	19.592	9.798	-3.067	1.704		1.035	-4.323	8.409	11.283
6.215	2.859	27.255	5.458	26.92	20.439	2.621	5.193	19.478	12.756	35.017	2.771	20.471	14.92
11.731	4.246		16.322	9.866	9.46	11.221	1.713	3.07	12.541	11.002	1.809	6.387	2.833
4.259	4.061		7.738	19.201	32.58	15.234	4.741	7.488	24.219	15.323	12.062	32.858	8.901
15.098	6.743	11.155	1.336	15.798	22.115	9.149	22.881	0.114	13.298	2.656	-15.747	35.526	35.526
5.321	2.817		16.913	1.154	3.358	4.822		-1.652	2.668	-14.165	-29.324	4.628	8.847
-3.011	2.137		3.488	2.874	1.329	-3.444		-6.608	3.966	-4.066	-7.911	6.428	-1.516
-1.437	0.119		-4.582	5.407	17.465	9.388		0.323	9.551	3.169	-8.132	6.366	2.165
3.884	4.285		24.477	3.202	4.224	4.131	19.576	-1.855	13.041	15.84	7.646	5.193	6.141
13.441	5.562			1.58	8.956	19.666		-0.407		0.823	1.443	13.209	10.166
9.015	9.013			1.066	9.462	18.183	4.754	-0.168		13.564	-9.473	4.35	3.718
4.849	16.879		5.755	9.043	13.975	13.204	9.318	2.035	3.279	3.038	-1.845	13.058	12.095
6.214	12.859	27.35	5.688	24.644	13.579	8.51		7.205		7.85	3.721	19.506	6.968
12.776	7.131		12.047	13.59	8.535	4.582	-4.448	-6.822	10.736	9.717	-7.617	10.164	2.93
4.529	6.079		-0.804	8.117	8.761	10.966		-2.052		-0.195	3.823	12.535	13.575

FIG. 39 (Continued)

driver_POT1	driver_RFX7	driver_RP515	driver_SAMHD1	driver_SF3B1	driver_TP53	driver_ZC3H18	driver_ZMYM3	driver_gain_7q22.1	driver_gain_15q24.2
17.835	2.275	12.834	14.817	2.658	7.178	13.57	7.86	14.953	14.541
14.371	-0.058	0.054	8.333	5.52	4.777	8.136	5.673	2.442	3.769
5.386	-2.724	-3.876	-2.496	6.856	11.191	-0.519	-2.224	12.657	10.233
6.554	41.218	-4.262	27.036	9.009	31.153	9.023	23.595	36.428	30.551
10.918	6.685	-0.641	6.298	9.942	11.01	7.304	3.595	13.738	19.466
-1.996	-8.023	-3.251	4.181	-0.899	-0.6	8.41	-7.053	4.079	12.153
2.832	0.872	3.723	5.407	3.714	-0.359	2.502	-0.343	2.609	3.116
3.541	5.998	-2.511	9.995	10.32	23.18	10.51	-1.99	4.352	15.893
7.341	19.167	-16.171	13.091	8.017	36.947	7.281	1.636	31.636	41.205
9.449	9.926	41.905	16.972	6.033	31.532	4.258	-3.018	27.176	15.628
2.677	12.771	9.5	6.302	8.225	25.344	9.725	5.981	27.696	17.025
0.685	7.046	-4.88	8.811	5.885	29.653	8.081	5.811	27.582	15.887
4.183	-0.672	1.875	-2.28	2.488	1.634	4.841	-0.4	2.121	10.792
2.191	1.565	8.707	2.195	2.06	1.222	7.384	-1.722	4.602	5.329
-1.428	-0.282	5.011	4.922	-1.11	9.237	7.186	-0.282	3.071	5.69
8.861	23.578	-7.115	-0.77	7.807	20.01	16.399	23.578	14.111	30.296
7.757	6.099	8.166	15.985	4.169	12.495	9.69	8.686	28.902	21.835
8.373	7.604	-4.516	12.499	10.17	26.483	6.475	9.458	25.079	12.701
-3.508	2.647	-0.704	4.251	-0.963	1.638	7.818	2.647	3.968	6.918
-1.384	0.294	4.999	7.874	1.43	0.138	5.781	-0.732	7.031	6.872
2.936	-5.032	-16.61	3.636	1.832	2.852	2.473	-5.032	3.416	11.241
9.313	8.483	14.42	7.203	17.174	5.577	26.92	14.193	15.418	15.926
1.713	0.327	0.853	8.632	4.969	10.684	9.866	0.327	6.162	9.743
4.741	6.387	12.062	35.683	8.389	2.534	19.201	3.447	13.262	32.329
20.271	15.098	-30.546	17.492	6.704	4.258	15.798	4.05	17.708	7.114
-2.679	-5.612	-29.324	1.667	-1.361	1.579	1.154	-5.228	8.66	0.984
-6.37	-9.94	-14.386	4.38	-7.761	-5.162	2.874	-6.488	4.375	4.475
-0.338	-5.495	-8.132	4.999	-2.666	0.805	5.407	-3.777	1.525	3.664
7.359	2.538	5.974	5.027	6.144	3.833	3.202	3.699	7.235	-0.237
5.046	-0.952	2.082	10.69	2.387	18.667	1.58	-0.952	4.76	7.74
6.529	-1.157	-15.058	3.523	4.256	15.457	1.066	-1.157	11.602	6.637
7.441	-0.756	4.954	12.627	5.691	11.736	9.043	-0.756	13.895	23.15
30.551	13.176	10.915	33.635	6.342	3.131	24.644	10.937	9.978	12.949
-3.737	11.017	-23.668	13.964	-5.253	10.505	13.59	10.505	12.895	6.894
0.117	5.859	6.849	8.638	0.463	8.119	8.117	5.859	4.254	8.267

FIG. 39 (Continued)

driver_loss_3p22.3	driver_loss_3p21.31	driver_loss_3p13	driver_loss_4q35.1	driver_loss_5p15.33	driver_loss_6q21	driver_loss_7p22.2	driver_loss_7q11.23b	driver_loss_7q11.23a	driver_loss_7q36.1
18.434	9.677	15.025	10.813	8.163	9.846	9.677	10.813	10.813	5.385
6.825	1.118	14.371	5.957	0.975	0.334	1.407	5.957	5.957	0.975
4.619	7.267	-13.508		9.411	10.161	9.411			15.694
36.682	10.512	27.273	21.969	16.088	44.353	15.702	21.969	21.969	23.465
9.724	11.332	10.096	24.93	12.154	16.743	12.154	24.93	24.93	16.052
4.253	2.672	1.986	9.876	1.347	3.435	1.626	9.876	9.876	5.806
4.263	3.805	4.547	-1.44	3.876	-0.913	5.617	-1.44	-1.44	1.761
4.547	6.432	14.491		5.179	7.083	5.186			8.725
28.766	25.162	-8.269	9.53	15.967	32.882	14.715	9.53	9.53	32.452
11.722	15.829	-5.559		17.538	29.153	16.763			31.631
14.944	15.175	13.19	17.178	15.175	24.892	15.175	17.178	17.178	24.848
7.486	8.175	17.096	1.575	9.909	41.421	9.909	1.575	1.575	28.879
1.121	2.366	6.508	11.79	3.382	4.112	3.528	11.79	11.79	2.835
5.707	3.327	3.281	13.455	2.648	4.193	6.706	13.455	13.455	2.153
3.739	2.177	-3.516		2.303	5.029	4.017			2.265
12.201	7.63	11.176		16.63	12.326	18.912			10.292
22.822	2.786	7.944	10.817	4.117	20.558	4.117	10.817	10.817	16.526
9.832	20.153	9.91		22.869	22.738	22.869			26.711
3.227	1.557	4.164		0.136	5.093	0.136			2.298
7.031	-2.825	-1.209	2.502	1.039	1.097	2.535	2.502	2.502	2.663
5.401	3.568	-1.115		1.636	2.398	2.33			0.855
14.027	43.359	5.193	17.174	32.288	12.215	20.637	17.174	17.174	38.491
6.162	6.171	1.713	3.599	10.5	6.365	11.854	3.599	3.599	6.689
15.938	11.156	4.741		16.095	14.956	14.956			9.033
11.489	5.847	11.825	1.619	11.516	24.198	11.516	1.619	1.619	23.927
3.021	-3.537	-3.717		2.741	7.081	4.786			5.434
5.815	-4.897	-8.169	-1.714	-3.166	2.175	-3.166	-1.714	-1.714	2.175
-0.525	0.967	2.546		3.883	5.988	1.02			3.883
7.235	8.805	11.926	20.689	8.618	10.279	9.08	20.689	20.689	17.026
6.094	4.511	1.824		6.134	1.076	6.134			1.541
1.702	10.755	4.543		12.851	11.702	11.896			11.896
11.097	7.713	8.047	-0.172	5.241	14.078	4.071	-0.172	-0.172	18.228
13.748	13.748	6.655	5.559	10.127	6.622	9.644	5.559	5.559	12.502
16.215	-2.89	0.568	19.337	4.6	23.694	6.075	19.337	19.337	5.567
4.254	2.711	-1.697		4.49	1.604	1.811			1.8

FIG. 39 (Continued)

driver_loss_9p21.3	driver_loss_9q34.3	driver_loss_10p12.2	driver_loss_10q24.2	driver_loss_10q24.32	driver_loss_11q22.3	driver_loss_12p13.31a	driver_loss_13q14.13	driver_loss_13q14.3
19.314	4.782	6.887	9.973	11.127	2.499	7.321	8.788	11.667
16.389	5.621	1.118	2.229	4.519	4.127	1.118	4.585	4.6
	-0.189	7.637	4.078	-3.628	7.207	8.251	4.532	4.581
10.588	3.597	16.088	24.448	28.389	11.618	13.443	23.557	16.626
3.772	3.425	8.443	9.526	13.537	4.332	10.145	9.658	8.957
7.271	4.497	-1.299	-2.455	-2.341	-1.276	-0.214	4.901	2.487
19.771	0.745	3.859	2.672	2.136	4.162	5.617	3.837	2.926
7.594	8.904	5.665	5.242	5.598	10.32	5.66	9.69	7.753
13.719	12.745	10.42	6.362	0.823	21.846	8.283	32.882	19.826
9.308	5.692	11.886	11.056	-0.101	7.626	14.169	13.668	11.643
	2.75	11.116	16.099	20.219	10.921	9.918	11.289	11.664
13.669	8.77	8.175	7.046	3.531	11.62	8.788	11.883	8.598
6.215	5.896	2.103	3.46	4.776	0.723	3.742	3.307	2.879
26.032	-2.285	3.538	3.538	-4.01	2.243	4.786	11.588	8.324
14.875	-1.004	1.599	1.025	-1.25	-0.109	2.177	10.922	5.026
21.788	6.62	21.896	21.896	16.096	13.28	20.455	19.377	15.971
	7.914	2.786	6.328	6.328	5.169	2.786	9.332	11.977
	7.602	15.429	16.275	22.357	9.72	20.153	14.789	12.62
1.572	0.92	0.072	2.647	12.231	1.327	-5.975	0.711	0.952
17.259	-1.941	-1.477	-1.477	-21.862	1.725	-5.105	0.564	1.289
14.824	0.816	1.788	5.991	3.827	1.138	3.84	8.275	6.892
4.426	11.391	32.288	10.256	9.765	10.687	42.547	22.515	17.872
22.351	1.713	10.685	11.538	6.797	5.58	11.854	8.301	7.507
1.545	5.003	13.301	12.848	14.87	8.819	19.672	14.843	13.767
14.51	10.789	8.104	4.136	-6.605	16.199	6.704	8.258	7.283
25.78	-1.652	-1.181	-0.649	-7.07	-0.847	-0.47	2.72	0.979
3.488	-6.608	-7.713	-11.42	-30.081	-6.891	-7.713	0.146	-1.391
-4.582	0.323	1.02	1.02	3.307	-1.68	3.781	7.396	3.565
29.928	2.861	8.178	7.909	8.805	5.344	9.08	10.803	5.498
	-0.407	3.425	4.324	1.824	2.387	9.983	6.973	6.679
	1.397	12.252	8.076	4.315	3.718	13.564	10.594	5.638
3.302	6.991	3.038	2.148	1.929	6.829	3.077	7.626	8.472
4.643	7.205	13.176	11.557	4.202	9.221	12.163	20.208	14.939
12.047	-5.782	3.151	7.382	-1.88	-1.94	0.956	13.77	6.073
-0.804	-2.052	4.29	5.889	-1.697	2.166	4.29	6.917	5.275

FIG. 39 (Continued)

driver_loss_14q32.12	driver_loss_14q32.33	driver_loss_15q15.1a	driver_loss_15q15.1b	driver_loss_15q26.1	driver_loss_16p11.2	driver_loss_16q22.1	driver_loss_17p13.3	driver_loss_17p13.1
11.062	11.505		11.062	11.137	10.005	8.049	7.321	7.008
5.015	1.144	14.371	-3.139	8.961	22.324	1.509	1.118	6.648
7.267	16.907		6.104	-2.224		7.637	8.251	21.586
13.829	27.914	10.806	5.274	12.23	28.483	16.088	13.443	48.981
7.954	16.245	6.727	16.814	-0.483	17.964	10.383	10.383	19.171
1.833	4.055		-2.341	-6.493		-0.214	-0.214	2.683
7.716	3.575	2.832	3.433	-3.825	29.569	4.545	5.617	5.024
14.854	5.12	14.899	3.896	-8.962		9.559	5.66	20.932
18.247	19.225		2.947	-8.375	21.605	8.283	8.283	35.455
18.155	36.39	5.936	23.056	-5.455	22.587	11.722	14.159	29.991
15.175	34.753	3.693	20.096	-2.205		10.843	9.918	40.075
8.788	33.328	20.002	3.531	-5.05		6.456	8.788	33.326
-2.886	2.443	7.446	7.126	0.733		3.742	3.742	2.194
-0.033	1.493		-4.521	-3.991		3.277	4.786	5.496
2.177	8.035	-6.14				1.195	2.177	7.573
-4.122	15.443	8.194				20.455	20.455	14.738
2.786	25.984	7.757	-7.058	8.686	-1.811	3.399	2.786	15.053
22.869	30.436	7.646	26.625	10.525		10.556	18.449	33.776
7.995	3.896	3.047				2.313	-5.975	3.546
-2.544	8.964	-1.209	-21.862	-6.451		2.192	-5.195	14.449
1.035	2.275	-3.067				10.968	6.584	-2.746
42.547	15.618	5.193	43.359	19.327	36.529	32.288	42.547	5.161
9.358	6.689	1.713	6.797		18.432	10.481	11.854	12.49
22.118	15.044	4.741	29.869	2.534		20.6	20.6	-0.57
11.627	18.002	22.881	-20.416	-1.388	21.062	7.035	6.704	20.716
-0.47	12.563		-10.951	-2.215	4.545	0.551	-0.47	11.028
-4.897	1.687		-34.26	-4.799		-7.713	-7.713	-5.263
6.962	4.461		4.33	-1.37		1.02	3.781	-1.437
8.723	5.056	19.576	8.805	10.357	6.318	8.177	9.08	2.999
5.912	2.327					9.983	9.983	18.667
12.354	12.248	4.754				4.635	11.626	13.166
8.488	19.79	9.318	1.929			3.051	3.051	8.818
21.222	6.622		4.202	0.726	12.163	12.163	12.163	2.677
7.464	7.561	-4.448	-13.035	10.505	22.732	0.956	0.956	12.776
8.065	3.373					4.782	4.29	1.129

FIG. 39 (Continued)

driver_loss_17q11.2	driver_loss_17q23.1	driver_loss_17q25.1	driver_loss_18q21.2	driver_loss_19p13.11	driver_loss_20p11.22	driver_tri_12	driver_gain_2p	driver_loss_11q	driver_loss_17p
19.314	5.583	11.505	15.025	11.505	11.476	14.394	2.499		13.299
16.389	4.23	-0.189	15.898	3.799	-2.193	5.729	-1.373	14.371	4.508
	21.586	20.93	-13.508	20.93	13.514	6.315	7.028		
10.588	64.092	36.428	49.313	35.715	25.994	19.432	5.102	10.806	
3.772	21.845	25.205	11.913	18.939	19.556	15.286	7.121	6.727	
7.271	1.291	4.079	1.986	5.127	1.021	3.654	-2.611		
19.771	3.804	1.761	6.392	1.761	2.103	5.064	5.719	2.832	-0.919
7.594	25.597	4.352	11.653	4.352	4.352	17.787	5.186	14.899	
13.719	40.593	40.462	-8.269	42.751	18.834	13.503	3.846		
9.308	46.62	47.671	-16.451	47.671	33.889	17.669	13.418	5.936	
	40.075	37.817	21.208	35.012	27.427	20.352	8.456	3.693	
13.669	39.185	46.073	3.906	47.317	28.978	17.251	-1.492	20.002	
6.215	1.123	2.857	4.729	2.857	3.382	1.123	-0.903	7.446	
26.032	0.352	1.493	3.281	11.134	0.845	9.736	-1.945		
14.875	5.072	2.983	-1.25	2.983	2.983	9.235	-1.103	-6.14	
21.788	12.445	14.111	16.096	14.111	14.111	12.445	9.425	8.194	
	15.053	38.796	15.164	38.154	13.419	18.994	9.606	7.757	14.592
	33.776	34.762	17.528	34.762	31.576	19.396	11.395	7.646	
1.572	4.61	7.03	12.231	7.03	7.03	3.529	-0.113	3.047	
17.259	14.193	6.061	-14.888	12.904	-9.432	13.78	-0.273	-1.209	
14.824	-5.15	-4.671	3.827	-4.671	-4.671	6.048	9.12	-3.067	
4.426	6.976	16.631	8.506	22.204	28.54	10.341	21.276	5.193	3.454
22.351	9.243	6.689	0.314	13.247	6.793	12.164	4.224	1.713	
1.545	-0.57	14.956	-1.211	14.956	18.568	10.499	13.605	4.741	
14.51	20.795	27.676	-8.078	37.307	5.621	7.648	16.794	22.881	1.336
25.78	-7.193	13.065	-3.717	13.065	2.622	2.064	0.424		
3.488	-6.898	2.939	-8.169	2.939	-14.542	1.357	-7.618		
-4.582	-0.308	3.883	2.546	3.883	3.883	3.808	-2.379		
29.928	0.663	5.582	4.344	9.284	8.342	7.247	1.06	19.576	
	18.667	2.789	1.824	2.789	2.789	14.445	6.093		
	13.166	12.201	4.315	12.201	12.201	9.849	3.718	4.754	
3.302	11.736	31.224	2.055	26.596	14.206	8.004	6.199	9.318	
4.643	2.105	6.622	6.655	18.989	4.883	4.664	3.961		
12.047	18.515	10.479	18.105	13.625	0.998	12.698	-7.813	-4.448	
-0.804	3.776	5.813	-1.697	5.813	5.813	1.818	5.275		

FIG. 39 (Continued)

driver_loss_17p	driver_loss_4p	driver_loss_6q	driver_loss_8p	driver_IGLV321_R110
13.299	13.299	12.834	-1.379	12.834
4.508	4.508	0.054	15.456	0.054
		-3.876	8.643	-3.876
		-4.262	8.584	-4.262
		-0.641	4.332	-0.641
		-3.251	11.5	-3.251
-0.919	-0.919	3.723	3.436	3.723
		-2.511	18.642	-2.511
		-16.171	25.162	-16.171
		-41.905	9.332	-41.905
		9.5	9.496	9.5
		-4.88	8.788	-4.88
		1.875	-8.76	1.875
		8.707	4.568	8.707
		5.011	1.085	5.011
		-7.115	2.358	-7.115
14.592	14.592	8.166	2.786	8.166
		-4.516	15.479	-4.516
		-0.704	-7.493	-0.704
		4.999	-2.52	4.999
		-16.61	1.035	-16.61
3.454	3.454	14.42	69.153	14.42
		0.853	7.597	0.853
		12.062	0.282	12.062
1.336	1.336	-30.546	6.704	-30.546
		-29.324	-7.471	-29.324
		-14.386	-4.897	-14.386
		-8.132	3.247	-8.132
		5.974	30.882	5.974
		2.082	0.823	2.082
		-15.058	8.204	-15.058
		4.954	8.86	4.954
		10.915	29.693	10.915
		-23.668	-5.863	-23.668
		6.849	-0.195	6.849

FIG. 39 (Continued)

Median delta-priming across healthy donors per normal cell type						
drug_name	CD14	CD19	CD3		drug_name	All_normals
A-1331852	-3.724	-1.868	-10.174		A-1331852	-6.121
AZD5991	1.2	-0.814	1.702		AZD5991	0.331
AZD8055	-10.788	9.358	-4.936		AZD8055	-2.629
Abexinostat	-4.827	-2.234	9.98		Abexinostat	3.559
Acalabrutinib	5.46	3.108	-0.687		Acalabrutinib	2.966
Azacitidine	-11.19	1.332	-15.909		Azacitidine	-6.202
Bendamustine	1.29	-2.145	-3.759		Bendamustine	-3.27
Carfilzomib	-28.732	-3.25	-20.299		Carfilzomib	-13.865
Cerdulatinib	0.545	-2.801	-19.616		Cerdulatinib	-6.598
Dasatinib	-14.601	-3.11	-3.481		Dasatinib	-5.002
Duvelisib	0.453	-7.191	0.804		Duvelisib	-1.655
Entospletinib	-23.528	-0.25	-6.018		Entospletinib	-7.957
Erastin	3.281	-0.404	0.385		Erastin	0.483
Fludarabine	-12.283	-1.727	-10.462		Fludarabine	-7.54
GSK690693	-3.886	3.559	-5.933		GSK690693	-1.552
Gandotinib	9.113	-0.061	0.863		Gandotinib	2.471
Ibrutinib	-4.029	-4.199	-9.168		Ibrutinib	-6.942
Idelalisib	1.381	2.416	-4.799		Idelalisib	0.86
JQ1	-19.288	9.74	-9.268		JQ1	-1.76
Lenalidomide	-10.628	4.371	-8.797		Lenalidomide	-8.719
MK-2206	-7.28	5.021	-8.897		MK-2206	-3.669
Navitoclax	-3.48	-0.479	-9.415		Navitoclax	-3.245
Nirogacestat	-15.91	-6.443	-8.365		Nirogacestat	-8.717
Nutlin-3	-14.725	-6.812	-23.043		Nutlin-3	-11.098
Onalespib	-3.855	-3.727	-7.234		Onalespib	-4.38
Osimertinib	-18.535	7.349	-20.673		Osimertinib	-4.553
Ricolinostat	-0.729	9.583	-3.394		Ricolinostat	1.942
Ruxolitinib	-8.991	-0.46	-19.663		Ruxolitinib	-8.991
Selinexor	-10.079	-0.809	-5.962		Selinexor	-5.346
Trametinib	2.252	11.446	-5.208		Trametinib	1.405
Umbralisib	5.35	-0.069	0.507		Umbralisib	2.325
Vecabrutinib	-3.53	6.157	-1.283		Vecabrutinib	-0.097
Venetoclax	-0.68	50.332	7.477		Venetoclax	4.838
Vorinostat	-6.793	10.602	3.043		Vorinostat	3.315
Voruciclib	-9.315	14.071	-10.078		Voruciclib	-2.36

FIG. 40

drug_name	M-CLL	U-CLL	i-CLL	m-CLL	n-CLL	EC-i	EC-m1	EC-m2	EC-m3	EC-m4	EC-o	EC-u1	EC-u2
A-1331852	11.892	11.908	12.834	11.678	11.908	8.163	10.439	8.778	12.843	13.64	13.496	8.904	20.138
AZD5991	4.157	5.486	3.686	3.995	5.502	3.072	0.845	5.762	4.767	3.984	5.454	5.289	7.364
AZD8055	3.827	3.552	2.465	4.429	6.211	4.247	1.718	2.47	1.229	3.813	5.104	4.941	8.329
Abexinostat	19.374	16.598	9.577	20.399	16.043	8.544	17.78	43.262	24.255	12.858	26.336	14.285	13.773
Acalabrutinib	8.652	9.263	9.902	8.32	9.263	3.981	3.24	12.829	3.692	7.728	10.809	8.57	13.349
Atorvastatin	5.836	3.918	8.226	5.836	3.763	3.167	1.105	15.045	4.757	6.122	8.21	4.379	0.497
Azacitidine	2.152	1.269	0.861	2.805	0.432	1.906	1.751	3.845	2.763	2.757	2.708	-1.139	2.115
Bendamustine	2.615	3.264	4.13	2.147	1.959	8.51	-0.619	5.064	4.657	1.08	1.462	2.01	7.601
Carfilzomib	8.689	5.183	10.782	7.474	6.773	4.231	11.241	14.484	3.485	8.256	7.61	5.183	18.871
Cerdulatinib	14.444	11.29	18.509	13.991	13.503	15.967	16.913	4.83	13.813	13.959	23.712	10.886	15.039
Crizotinib	-0.941	-5.176	-2.392	-1.116	-2.805	-20.533	-0.927	3.81	-4.03	-1.505	0.413	-2.574	-7.395
Dasatinib	10.851	11.445	10.999	10.851	14.726	6.995	9.974	8.513	13.387	9.51	11.415	11.206	19.779
Duvelisib	12.376	10.231	12.833	12.032	9.396	9.5	14.945	23.755	11.556	11.635	11.272	9.716	10.794
Entospletinib	8.195	8.176	8.331	8.195	8.176	5.216	-0.032	19.676	7.29	7.879	17.024	5.982	12.962
Erastin	2.491	2.234	2.872	2.408	1.825	1.875	3.225	2.799	0.178	3.214	2.414	1.958	0.309
Fludarabine	9.622	3.936	11.085	8.965	2.243	6.372	5.786	9.624	9.558	10.937	7.322	2.243	7.5
GSK690693	5.535	2.303	10.101	4.061	1.938	2.177	1.891	10.013	-1.799	6.768	12.232	1.938	7.046
Gandotinib	17.845	12.768	18.495	16.873	12.768	-5.218	13.876	14.153	5.772	20.261	29.895	14.567	8.548
Ibrutinib	11.977	12.962	9.855	12.747	12.72	3.148	12.393	8.828	15.365	11.407	15.777	8.733	22.96
Idelalisib	12.042	11.931	19.34	10.61	11.395	3.915	8.282	15.039	8.198	16.885	9.661	11.288	15.952
JQ1	1.149	1.828	2.94	0.976	1.527	-3.559	-1.2	4.389	-0.992	2.323	-0.49	-0.113	3.595
Lenalidomide	2.559	1.128	4.547	2.187	1.109	3.101	-1.24	11.65	3.852	0.728	4.784	0.396	4.552
MK-2206	7.384	3.692	7.378	7.98	3.692	-4.684	5.371	4.982	2.173	8.838	9.192	5.546	10.009
Navitoclax	18.724	10.17	20.414	18.201	7.642	36.529	20.92	4.532	24.275	26.071	13.379	9.473	17.15
Nirogacestat	9.01	4.931	7.651	9.306	4.931	7.52	5.813	12.164	6.845	9.07	7.5	3.85	8.632
Nutlin-3	18.813	11.044	19.847	15.905	12.981	7.181	31.071	6.231	12.423	25.3	16.231	11.044	37.328
Onalespib	5.939	5.772	5.49	5.976	12.206	5.847	0.114	7.648	12.71	2.762	10.637	7.061	-1.158
Osimertinib	1.176	0.722	0.87	1.621	1.215	-5.247	-0.272	-0.371	-0.498	0.559	3.885	1.214	2.552
Ponatinib	0.509	-8.398	-7.784	1.181	0.436	-22.007	-4.146	4.627	0.027	-0.901	-0.778	2.079	4.508
Rapamycin	10.498	3.339	19.044	8.578	3.339	15.674	3.859	5.091	2.305	15.664	7.43	3.339	13.6
Ricolinostat	-1.124	-4.548	-7.994	0.578	-4.548	-10.23	-6.778	-1.134	-0.11	-0.328	2.749	-6.54	4.054
Ruxolitinib	3.752	0.91	2.679	3.752	0.316	-1.75	5.128	0.132	0.505	7.912	3.9	-0.072	7.753
Selinexor	7.142	5.193	7.411	6.673	5.066	8.235	10.963	5.194	4.288	6.715	7.155	5.066	14.755
Sorafenib	-2.906	-5.988	-9.168	-2.581	-4.852	-11.019	-4.169	-2.124	-4.419	-2.939	-4.866	-4.266	-7.015
Sunitinib	5.129	4.313	10.607	4.908	3.813	-7.788	0.124	5.429	2.908	5.166	9.938	5.829	4.644
Trametinib	6.413	4.372	7.096	6.347	4.372	1.23	0.124	2.327	3.404	5.239	8.337	5.346	17.505
Umbralisib	7.773	3.786	12.319	5.69	3.864	-3.959	0.348	10.335	5.036	8.257	7.436	4.086	5.684
Vecabrutinib	7.356	6.184	6.962	7.987	6.184	6.776	7.873	2.365	8.493	9.441	7.617	6.605	14.365
Venetoclax	15.091	8.574	14.804	14.939	8.574	15.93	12.492	1.476	27.262	14.947	15.357	8.574	21.606
Vorinostat	7.212	4.514	0.886	7.966	4.251	-5.863	-6.263	18.351	12.951	2.17	14.482	1.743	8.903
Voruciclib	4.706	5.275	6.217	4.739	3.672	6.028	-1.396	0.909	1.225	7.667	8.119	5.06	4.37
Zanubrutinib	7.403	10.614	10.565	7.257	9.813	8.527	1.802	13.906	4.205	6.038	11.765	10.614	11.733

FIG. 41

driver_CUL9	driver_DICER1	driver_FBXW7	driver_GNB1	driver_GSR	driver_ITIH2	driver_ITPKB	driver_KLHL6	driver_KMT2D	driver_MAP2K1
17.493	12.02	10.076	9.738	11.968	16.962	13.57	15.981	5.353	
4.16	6.697	5.65	1.762	4.097	6.819	8.136	8.789	1.336	14.371
3.425	1.28	7.37	12.607		-1.664	-0.519	9.731	11.191	
32.243	14.4	31.852	26.876		12.041	9.023	20.603	31.153	10.806
1.523	13.741	7.819	14.369		25.31	7.304	16.617	11.01	6.727
-6.694	5.728	4.358	3.156		13.203	7.633	15.155	16.472	
0.429	9.085	0.452	-0.727		7.271	8.41	5.399	1.658	
12.161	-2.646	1.442	3.374	-3.527	-0.93	2.502	8.279	-0.458	2.832
13.265	12.683	7.392	0.634		11.1	10.51	8.445	25.243	14.899
16.913	20.262	19.421	24.98		11.693	7.281	30.723	47.482	
1.275	5.137	1.312	-3.315		10.249	-6.299	-1.394	4.393	-1.037
2.543	7.644	13.057	3.845		10.122	4.258	20.871	31.741	5.936
14.945	10.458	12.771	23.215		14.148	9.725	16.449	25.344	3.693
-2.599	19.293	7.879	10.961		20.104	8.081	4.957	29.653	20.002
-0.027	6.171	1.363	0.36		6.393	4.841	2.471	2.345	7.446
18.757	11.49	4.97	7.601		26.032	7.384	12.692	3.991	
5.613		5.072	6.291		14.875	7.186	14.027	14.759	-6.14
24.46		17.887	40.328		21.788	16.399	25.818	30.69	8.194
13.33	15.777	13.103	20.273	19.395	21.379	9.69	18.995	16.27	7.757
10.52	1.762	14.013	17.586		17.449	6.475	18.691	31.312	7.646
-0.597		3.899	-0.179		1.572	7.818	-0.605	-0.775	3.047
-0.204	15.774	11.508	-0.572		17.259	5.781	6.722	-2.974	-1.209
7.549		1.596	11.662		14.824	2.473	19.592	9.798	-3.067
22.633	12.756	6.215	2.859	27.255	5.458	26.92	20.439	2.621	5.193
10.197	12.541	11.731	4.246		16.322	9.866	9.46	11.221	1.713
39.099	24.219	4.259	4.061		7.738	19.201	32.58	15.234	4.741
26.486	13.298	15.098	6.743	11.155	1.336	15.798	22.115	9.149	22.881
-2.554	2.668	5.321	2.817		16.913	1.154	3.358	4.822	
0.199	8.368	1.455	4.408		4.529	-8.927	7.954	11.627	-16.583
8.866	5.786	-2.131	5.172		8.805	11.101	24.34	9.105	1.189
-7.423	3.966	-3.011	2.137		3.488	2.874	1.329	-3.444	
6.996	9.551	-1.437	0.119		-4.582	5.407	17.465	9.388	
4.649	13.041	3.884	4.285		24.477	3.202	4.224	4.131	19.576
-3.285	-4.763	-3.216	33.43			14.096	-7.157	6.693	
3.673	8.25	-2.712	-1.39		4.45	4.797	22.933	13.078	
7.781		13.441	5.562			1.58	8.956	19.666	
5.675		9.015	9.013			1.066	9.462	18.183	4.754
15.5	3.279	4.849	16.879		5.755	9.043	13.975	13.204	9.318
15.537		6.214	12.859	27.35	5.688	24.644	13.579	8.51	
0.498	10.736	12.776	7.131		12.047	13.59	8.535	4.582	-4.448
12.166		4.529	6.079		-0.804	8.117	8.761	10.966	
3.775	1.217	2.539	15.196		9.266	6.053	22.929	22.717	-0.713

FIG. 41 (Continued)

driver_MAPK4	driver_MED1	driver_MYD88	driver_NOTCH1	driver_NRAS	driver_NXF1	driver_POT1	driver_RFX7	driver_RPS15	driver_SAMHD1	driver_SF3B1
4.782	12.02	8.836	18.187	13.519	11.114	17.835	2.275	12.834	14.817	2.658
-0.741	6.697	1.53	3.71	7.364	1.124	14.371	-0.058	0.054	8.333	5.52
-0.189	1.28	7.267	-3.876	15.129	18.131	5.386	-2.724	-3.876	-2.496	6.856
-1.551	14.4	17.512	-3.006	25.988	11.786	6.554	41.218	-4.262	27.036	9.009
3.064	13.741	15.312	9.789	4.741	4.928	10.918	6.685	-0.641	6.298	9.942
3.296	5.728	8.489	1.827	0.497	3.822	14.848	34.358	1.827	2.79	13.618
4.497	9.085	8.111	0.189	1.833	-0.545	-1.996	-8.023	-3.251	4.181	-0.899
-0.619	-2.646	0.933	-3.595	10.259	9.592	2.832	0.872	3.723	5.407	3.714
6.085	12.683	11.644	-2.511	15.685	7.31	3.541	5.998	-2.511	9.995	10.32
12.745	20.262	6.054	1.312	26.241	26.241	7.341	19.167	-16.171	13.091	8.017
-2.029	5.137	-4.371	-43.24	-7.099	-5.38	-2.306	-4.123	-43.24	-8.06	-2.306
5.692	7.644	16.621	-41.906	19.548	19.746	9.449	9.926	-41.906	16.972	6.033
0.929	10.458	10.398	-1.781	20.309	22.378	2.677	12.771	9.5	6.302	8.225
-1.197	19.293	14.481	1.528	13.429	12.96	0.685	7.046	-4.88	8.811	5.885
3.75	6.171	3.707	3.113	-1.602	1.712	4.183	-0.672	1.875	-2.28	2.488
-2.285	11.49	9.736	12.858	1.14	3.833	2.191	1.565	8.707	2.195	2.06
0.093		1.085	5.011	5.848	4.218	-1.428	-0.282	5.011	4.922	-1.11
6.249		2.358	1.857	8.618	16.721	8.861	23.578	-7.115	-0.77	7.807
7.914	15.777	1.773	14.657	25.372	21.467	7.757	6.099	8.166	15.985	4.169
7.278	1.762	22.869	-4.516	12.554	12.158	8.373	7.604	-4.516	12.499	10.17
-1.564		-7.493	-0.035	4.355	2.905	-3.508	2.647	-0.704	4.251	-0.963
-3.565	15.774	-2.118	-6.851	4.693	0.889	-1.384	0.294	4.999	7.874	1.43
1.704		1.035	-4.323	8.409	11.283	2.936	-5.032	-16.61	5.636	1.832
19.478	12.756	35.017	2.771	20.471	14.92	9.313	8.483	14.42	7.203	17.174
3.07	12.541	11.002	1.809	6.387	2.833	1.713	0.327	0.853	8.632	4.969
7.488	24.219	15.323	12.062	32.858	8.901	4.741	6.387	12.062	35.683	8.389
0.114	13.298	2.656	-15.747	35.528	35.528	20.271	15.098	-30.546	17.492	6.704
-1.652	2.668	-14.165	-29.328	4.628	8.847	-2.679	-5.612	-29.328	1.667	-1.361
-5.325	8.368	-17.472	-47.983	0.852	9.407	1.212	-46.830	-47.983	-14.385	-0.181
3.498	5.786	12.637	35.757	11.401	4.659	0.457	-30.172	35.757	7.889	3.339
-6.608	3.966	-4.066	-7.911	6.428	-1.516	-6.37	-9.94	-14.386	4.38	-7.761
0.323	9.551	3.169	-8.132	6.366	2.165	-0.338	-5.495	-8.132	4.999	-2.666
-1.855	13.041	15.84	7.646	5.193	6.141	7.359	2.538	5.974	5.027	6.144
-4.169	-4.763	-2.523	-23.702	-11.59	-1.678	5.35	-37.148	-23.702	-16.506	-0.478
-0.507	8.25	-0.852	-13.175	11.527	14.234	2.963	-45.238	-13.175	3.813	-0.341
-0.407		0.823	1.443	13.209	10.166	5.046	-0.952	2.082	10.69	2.387
-0.168		13.564	-9.473	4.35	3.718	6.529	-1.157	-15.058	3.523	4.256
2.035	3.279	3.038	-1.845	13.058	12.095	7.441	-0.756	4.954	12.627	5.691
7.205		7.85	3.721	19.506	6.968	30.553	13.176	10.915	33.635	6.342
-6.822	10.736	9.717	-7.617	10.164	2.93	-3.737	11.017	23.668	13.964	-5.253
-2.052		-0.195	3.823	12.535	13.575	0.117	5.859	6.849	8.638	0.463
0.823	1.217	0.763	16.708	11.717	15.979	6.583	-6.464	16.708	3.95	6.583

FIG. 41 (Continued)

age_above_60	Post_treatment	driver_ANK1	driver_ATM	driver_BCOR	driver_BIRC3	driver_BRCC3	driver_CARD11	driver_CHD2	driver_CNOT3
11.118	8.068	11.137	5.906	21.382	19.314	11.114	4.595	7.225	33.148
4.207	7.698	8.961	1.972	5.034	16.389	1.124	7.162	2.174	9.773
5.211	6.652	-2.224	8.643			18.131		12.655	
20.197	40.2	12.23	6.706	7.159	10.588	11.786	17.013	21.029	55.888
10.665	10.533	-0.483	7.121	17.009	3.772	4.928	9.942	14.495	19.218
6.031	4.263		6.347		13.203	3.822		8.254	
2.551	3.311	-6.493	-1.728	2.115	7.271	-0.545	14.178	0.896	4.681
3.383	2.81	-3.825	6.634	-4.628	19.771	9.592	1.992	4.037	-7.742
7.412	11.5	-8.962	6.44		7.594	7.31	14.899	12.802	
13.422	24.836	-8.375	23.172	13.503	13.719	26.241	4.403	13.497	10.168
-1.887	-4.361		-5.176		10.249	-5.38	-1.037	-0.448	
11.728	8.102	-5.455	17.239		9.308	19.746	5.936	27.296	
11.847	12.771	-2.205	10.308	-4.028		22.378	10.519	20.438	0.553
8.783	14.501	-5.05	8.788	7.231	13.669	12.96	15.067	17.251	18.086
2.863	2.933	0.733	1.712	4.17	6.215	1.712	7.446	2.194	7.355
6.94	4.772	-3.991	1.485	15.54	26.032	3.833	13.734	6.679	17.183
3.47	0.018		1.938	6.063	14.875	4.218	-6.14	5.174	
13.231	12.626		12.452	13.328	21.788	16.721	8.194	14.738	
11.059	11.017	8.686	10.831	17.213		21.467	6.399	15.338	25.282
12.042	12.459	10.525	11.395			12.158	7.646	18.139	
0.976	3.25		-1.23	-0.035	1.572	2.905	3.047	2.062	
2.104	1.144	-6.451	-1.834	-4.574	17.259	0.889	4.141	10.527	-2.118
6.667	0.626		5.546	8.636	14.824	11.283	-3.067	11.704	
13.883	10.253	18.327	38.177	-2.874	4.426	14.92	4.145	10.18	15.25
7.268	5.703		4.224	5.408	22.351	2.833	6.646	14.328	9.642
12.851	4.614	2.534	6.695		1.545	8.901	4.741	5.034	
4.695	12.516	-1.388	28.415	-8.147	14.51	35.526	7.283	11.516	8.295
1.176	-2.921	-2.215	0.014		25.78	8.847		2.762	
0.667	-12.211		6.714		4.529	9.407	16.583	6.852	
9.766	2.311		5.221		8.805	4.659	1.189	11.392	
-2.671	-4.066	-4.799	-3.764	-5.719	3.488	-1.516	16.339	-2.244	-1.506
1.316	-0.285	-1.37	1.414		-4.582	2.165		2.321	
5.694	8.076	10.357	6.141	20.702	29.928	6.141	12.568	7.909	19.794
-3.013	-4.275		0.218			-1.678		3.783	
4.793	3.431		4.588		4.45	14.234		4.508	
5.47	4.423		6.093	0.222		10.166		21.36	
5.162	4.543		4.385	2.128		3.718	4.754	10.789	
7.921	7.921		8.984	-2.906	3.302	12.095	0.951	11.736	-5.214
10.096	12.791	0.726	13.859	1.664	4.643	6.968	-1.072	13.19	20.372
6.246	13.701	10.505	-3.797	4.514	12.047	2.93	19.337	6.567	37.871
4.444	2.651		5.275	-1.494	-0.804	13.575		6.328	
9.975	7.35		10.336		9.266	15.979	-0.713	13.327	

driver_TP53	driver_ZC3H18	driver_ZMYM3	driver_gain_7q22.1	driver_gain_15q24.2	driver_gain_16p11.2	driver_gain_19p13.3	driver_loss_1p36.11	driver_loss_1p35.2
7.178	13.57	7.86	14.953	14.541	9.677	9.874	15.025	11.505
4.777	8.136	5.673	2.442	3.769	3.596	4.282	15.698	-0.189
11.191	-0.519	-2.224	12.657	10.233	7.97	6.055	-13.508	20.93
31.153	9.023	23.595	36.428	30.551	9.403	26.907	-49.333	36.428
11.01	7.304	3.595	13.738	19.466	9.903	8.279	11.913	25.205
16.472	7.633	-34.358	2.825	4.801	9.196	5.407	9.716	1.104
-0.6	8.41	-7.053	4.079	12.153	1.301	0.917	1.986	4.079
-0.359	2.502	-0.343	2.609	3.116	5.617	2.446	6.392	1.761
23.18	10.51	-1.99	4.352	15.893	8.068	7.539	11.653	4.352
36.947	7.281	1.636	31.636	41.205	13.719	9.932	-8.269	40.462
4.393	-6.299	-4.123	0.183	-11.679	-2.614	-0.341	-10.679	2.151
31.532	4.258	-3.018	27.176	15.628	13.503	9.308	-16.451	47.675
25.344	9.725	5.981	27.696	17.025	15.175	11.567	21.208	27.817
29.653	8.081	5.811	27.582	15.887	8.175	8.383	3.906	46.073
1.634	4.841	-0.4	2.121	10.792	3.528	2.333	4.729	2.857
1.222	7.384	-1.722	4.602	5.329	4.802	3.81	3.281	1.493
9.237	7.186	-0.282	3.071	5.69	4.402	4.684	-1.25	2.983
20.01	16.399	23.578	14.111	30.296	14.235	17.293	16.096	14.111
12.495	9.69	8.686	28.902	21.835	-0.131	11.444	15.164	38.796
26.483	6.475	9.458	25.079	12.701	22.869	10.288	17.528	34.762
1.638	7.818	2.647	3.968	6.918	-0.053	3.607	12.231	7.03
0.138	5.781	-0.732	7.031	6.872	-2.52	6.239	-14.888	6.061
2.852	2.473	-5.032	3.416	11.241	1.788	5.417	3.827	-4.671
5.577	26.92	14.193	15.418	15.926	43.359	11.228	8.506	16.631
10.684	9.866	0.327	6.162	9.743	11.002	8.826	0.314	6.689
2.534	19.201	3.447	13.262	32.329	7.738	12.13	-1.211	14.956
4.258	15.798	4.05	17.708	7.114	6.036	7.842	-8.078	27.678
1.579	1.154	-5.228	8.66	0.984	-3.537	1.428	-3.717	13.065
11.627	-9.927	-46.829	3.978	-4.94	-3.939	-0.592	20.413	3.978
9.105	11.101	-30.173	9.661	16.671	11.065	10.96	-8.914	6.624
5.162	2.874	-6.488	4.375	4.475	13.448	5.685	-8.169	2.939
0.805	5.407	-3.777	1.525	3.664	0.424	0.014	2.546	3.883
3.833	3.202	3.699	7.235	-0.237	24.293	5.222	4.344	5.582
6.693	14.096	-39.168	-6.233	-8.309	-2.523	-5.431	5.15	-4.325
13.078	4.797	-46.248	15.886	4.206	1.732	3.978	13.347	18.308
18.667	1.58	-0.952	4.76	7.74	0.823	7.967	1.824	2.789
15.457	1.066	-1.157	11.602	6.637	8.204	5.188	4.315	12.201
11.736	9.043	-0.756	13.895	23.15	3.051	3.44	2.055	31.224
3.131	24.644	10.937	9.978	12.949	8.311	8.148	6.655	6.622
10.505	13.59	10.505	12.895	6.894	-2.89	7.382	18.105	10.479
8.119	8.117	5.859	4.254	8.267	-0.68	4.492	-1.697	5.813
22.717	6.053	-6.464	22.749	11.526	1.547	5.974	13.906	32.152

FIG. 41 (Continued)

driver_loss_1q21.3	driver_loss_1q42.13	driver_loss_2p11.2	driver_loss_2q31.1	driver_loss_3p22.3	driver_loss_3p21.31	driver_loss_3p13	driver_loss_4q35.1	driver_loss_5p15.33
7.884	10.005	2.499	7.321	18.434	9.677	15.025	10.813	8.163
1.407	14.371	-1.373	0.975	6.825	1.118	14.371	5.957	0.975
8.251		7.028	8.5	4.619	7.267	13.508		9.411
10.512	13.03	5.102	22.427	36.682	10.512	27.273	21.969	16.088
8.119	9.283	7.121	10.145	9.724	11.332	10.096	24.93	12.154
6.912	2.341	6.347	2.518	3.962	4.462	9.716		3.104
1.082		-2.611	1.021	4.253	2.672	1.986	9.876	1.347
3.876	8.379	5.719	2.672	4.263	3.805	4.547	-1.44	3.876
5.66	14.899	5.186	5.242	4.547	6.432	14.491		5.179
7.58	21.605	3.846	17.919	28.766	25.162	-8.269	9.53	15.967
-2.614	-1.037	-5.176	-3.421	-1.548	-3.421	-3.702		-3.421
10.301	14.662	13.418	15.341	11.722	15.829	-5.559		17.538
9.918	3.693	8.456	13.836	14.944	15.175	13.19	17.178	15.175
8.788	20.002	-1.492	8.996	7.486	8.175	17.096	1.575	9.909
3.763	7.446	-0.903	2.835	1.121	2.366	6.508	11.79	3.382
6.77		-1.945	2.648	5.707	3.327	3.281	13.455	2.648
5.473	-6.34	-1.103	2.265	3.739	2.177	-3.516		2.303
20.455	8.194	9.425	19.357	12.201	7.63	11.176		16.63
2.786	4.595	9.606	4.117	22.822	2.786	7.944	10.817	4.117
18.449	7.646	11.395	20.153	9.832	20.153	9.91		22.869
-1.288	3.047	-0.113	0.911	3.227	1.557	4.164		0.136
2.192	-1.209	-0.273	0.294	7.031	-2.825	-1.209	2.502	1.039
9.035	-3.067	9.12	1.035	5.401	3.568	-1.115		1.636
27.62	8.694	21.276	19.231	14.027	43.359	5.193	17.174	32.288
12.283	9.64	4.224	9.761	6.162	6.171	1.713	3.599	10.5
15.004	4.741	13.605	14.956	15.938	11.156	4.741		16.095
6.704	22.881	16.794	14.296	11.489	5.847	11.825	1.619	11.516
0.551	4.545	0.424	0.551	3.021	-3.537	-3.717		2.741
-1.35	16.583	10.154	-3.702	3.094	-5.898	-18.657		-1.412
11.31	1.189	2.315	8.625	12.458	12.637	0.457		11.31
-5.812		-7.618	-4.502	5.815	-4.897	-8.169	-1.714	-3.166
0.781		-2.379	2.256	-0.525	0.967	2.546		3.883
12.733	11.934	1.06	8.178	7.235	8.805	11.926	20.689	8.618
-4.389		2.493	-6.347	-6.287	-4.275	5.15		-4.389
3.923		10.109	1.382	10.607	6.125	13.347		5.868
9.983		6.093	2.789	6.094	4.511	1.824		6.134
11.626	4.754	3.718	12.252	1.702	10.755	4.543		12.851
3.051	9.318	6.199	3.454	11.097	7.713	8.047	-0.172	5.241
9.644	12.163	3.961	11.583	13.748	13.748	6.655	5.559	10.127
0.205	5.343	-7.813	6.075	16.215	-2.89	0.568	19.337	4.6
1.6		5.275	4.49	4.254	2.711	-1.697		4.49
9.801	-0.713	12.315	9.801	9.861	8.315	9.259		11.628

driver_loss_6q21	driver_loss_7p22.2	driver_loss_7q11.23b	driver_loss_7q11.23a	driver_loss_7q36.1	driver_loss_9p21.3	driver_loss_9q34.3	driver_loss_10p12.2
9.846	9.677	10.813	10.813	5.385	19.314	4.782	6.887
0.334	1.407	5.957	5.957	0.975	16.389	5.621	1.118
10.161	9.411			15.694		-0.189	7.637
44.353	15.702	21.969	21.969	23.465	10.588	3.597	16.088
16.743	12.154	24.93	24.93	16.052	3.772	3.425	8.443
4.275	3.628			3.134	13.203	3.296	3.011
3.435	1.626	9.876	9.876	5.806	7.271	4.497	-1.299
-0.913	5.617	-1.44	-1.44	1.761	19.771	0.745	3.859
7.083	5.186			8.725	7.594	8.904	5.665
32.882	14.715	9.53	9.53	32.452	13.719	12.745	10.42
5.04	-0.444			-4.371	10.249	-1.77	-4.153
29.153	16.763			31.631	9.308	5.692	11.886
24.892	15.175	17.178	17.178	24.848		2.75	11.116
41.421	9.909	1.575	1.575	28.879	13.669	8.77	8.175
4.112	3.528	11.79	11.79	2.835	6.215	5.896	2.103
4.193	6.706	13.455	13.455	2.153	26.032	-2.285	3.538
5.029	4.017			2.265	14.875	-1.004	1.599
12.326	18.912			10.292	21.788	6.62	21.896
20.558	4.117	10.817	10.817	16.526		7.914	2.786
22.738	22.869			26.711		7.602	15.429
5.093	0.136			2.298	1.572	0.92	0.072
1.097	2.535	2.502	2.502	2.663	17.259	-1.941	-1.477
2.398	2.33			0.855	14.824	0.816	1.788
12.215	20.637	17.174	17.174	38.491	4.426	11.391	32.288
6.365	11.854	3.599	3.599	6.689	22.351	1.713	10.685
14.956	14.956			9.033	1.545	5.003	13.301
24.198	11.516	1.619	1.619	23.927	14.51	10.789	8.104
7.081	4.786			5.434	25.78	-1.652	-1.181
14.633	-0.178			-4.001	4.529	-6.169	-10.339
3.077	9.985			8.625	8.805	2.311	11.31
2.175	-3.166	-1.714	-1.714	2.175	3.488	-6.608	-7.713
5.988	1.02			3.883	-4.582	0.323	1.02
10.279	9.08	20.689	20.689	17.026	29.928	2.861	8.178
-1.909	-4.389			-2.523		-4.169	-6.494
12.008	4.566			9.322	4.45	-0.507	-1.72
1.076	6.134			1.541		-0.407	3.425
11.702	11.896			11.896		1.397	12.252
14.078	4.071	-0.172	-0.172	18.228	3.302	6.991	3.038
6.622	9.644	5.559	5.559	12.502	4.643	7.205	13.176
23.694	6.075	19.337	19.337	5.567	12.047	-5.782	3.151
1.604	1.811			1.8	-0.804	-2.052	4.29
17.967	11.628			19.417	9.266	0.823	3.705

driver_loss_10q24.2	driver_loss_10q24.32	driver_loss_11q22.3	driver_loss_12p13.31a	driver_loss_13q14.13	driver_loss_13q14.3	driver_loss_14q32.12	driver_loss_14q32.33
9.973	11.127	2.499	7.321	8.788	11.667	11.062	11.505
2.229	4.519	4.127	1.118	4.585	4.6	5.015	1.144
4.078	-3.628	7.207	8.251	4.532	4.581	7.267	16.907
24.448	28.389	11.618	13.443	23.557	16.626	13.829	27.914
9.526	13.537	4.332	10.145	9.658	8.957	7.954	16.245
3.011	9.716	3.983	3.818	9.569	5.764	2.218	7.447
-2.455	-2.341	-1.276	-0.214	4.901	2.487	1.833	4.055
2.672	2.136	4.162	5.617	3.837	2.926	7.716	3.575
5.242	5.598	10.32	5.66	9.69	7.753	14.854	5.12
6.362	0.823	21.846	8.283	32.882	19.826	18.247	19.225
-3.451	-10.678	-3.464	-4.153	-1.491	-1.831	-7.395	1.677
11.056	-0.101	7.626	14.169	13.668	11.643	18.155	36.39
16.099	20.219	10.921	9.918	11.289	11.664	15.175	34.753
7.046	3.531	11.62	8.788	11.883	8.598	8.788	33.328
3.46	4.776	0.723	3.742	3.307	2.879	-2.886	2.443
3.538	-4.01	2.243	4.786	11.588	8.324	-0.033	1.493
1.025	-1.25	-0.109	2.177	10.922	5.026	2.177	8.035
21.896	16.096	13.28	20.455	19.377	15.971	-4.122	15.443
6.328	6.328	5.169	2.786	9.332	11.977	2.786	25.984
16.275	22.357	9.72	20.153	14.789	12.62	22.889	30.436
2.647	12.231	1.327	-5.975	0.711	0.952	7.995	3.896
-1.477	-21.862	1.725	-5.105	0.564	1.289	-2.544	8.964
5.991	3.827	1.138	3.84	8.275	6.892	1.035	2.275
10.256	9.765	10.687	42.547	22.515	17.872	42.547	15.618
11.538	6.797	5.58	11.854	8.301	7.507	9.358	6.689
12.848	14.87	8.819	19.672	14.843	12.767	22.118	15.044
4.136	-6.605	16.199	6.704	8.258	7.283	11.627	18.002
-0.649	-7.07	-0.847	-0.47	2.72	0.979	-0.47	12.563
-10.471	-20.413	4.417	-6.291	-5.325	-0.654	-13.326	3.978
0.62	-8.914	3.339	12.637	7.286	7.517	13.849	11.34
-11.42	-30.083	-6.891	-7.713	0.146	-1.391	-4.897	1.687
1.02	3.307	-1.68	3.781	7.396	3.565	6.962	4.461
7.909	8.805	5.344	9.08	10.803	5.498	8.723	5.056
-6.63	5.15	-2.562	-4.389	-4.58	-2.562	-12.777	-3.033
2.965	13.347	-0.852	1.382	6.38	5.071	3.186	11.23
4.324	1.824	2.387	9.983	6.973	6.679	5.912	2.327
8.076	4.315	3.718	13.564	10.594	5.638	12.354	12.248
2.148	1.929	6.829	3.077	7.626	8.472	8.488	19.79
11.557	4.202	9.221	12.163	20.208	14.939	21.222	6.622
7.382	-1.88	-1.94	0.956	13.77	6.073	7.464	7.561
5.889	-1.697	2.166	4.29	6.917	5.275	8.065	3.373
10.286	13.906	5.815	9.801	7.501	8.796	0.376	28.194

driver_loss_15q15.1a	driver_loss_15q15.1b	driver_loss_15q26.1	driver_loss_16p11.2	driver_loss_16q22.1	driver_loss_17p13.3	driver_loss_17p13.1	driver_loss_17q11.2
	11.062	11.137	10.005	8.049	7.321	7.008	19.314
14.371	-3.139	8.961	22.324	1.509	1.118	6.648	16.389
	6.104	-2.224		7.637	8.251	21.586	
10.806	5.274	12.23	28.483	16.088	13.443	48.981	10.588
6.727	16.814	-0.483	17.964	10.383	10.383	19.171	3.772
			2.341	4.199	3.818	13.203	13.203
	-2.341	-6.493		-0.214	-0.214	2.683	7.271
2.832	3.433	-3.825	29.569	4.545	5.617	5.024	19.771
14.899	3.896	-8.962		9.559	5.66	20.932	7.594
	2.947	-8.375	21.605	8.283	8.283	35.455	13.719
-1.037				-4.153	-4.401	10.249	10.249
5.936	23.056	-5.455	22.587	11.722	14.169	29.991	9.308
3.693	20.096	-2.205		10.843	9.918	40.075	
20.002	3.531	-5.05		6.456	8.788	33.326	13.669
7.446	7.126	0.733		3.742	3.742	2.194	6.215
	-4.521	-3.991		3.277	4.786	5.496	26.032
-6.14				1.195	2.177	7.573	14.875
8.194				20.455	20.455	14.738	21.788
7.757	-7.058	8.686	-1.811	3.399	2.786	15.053	
7.646	26.625	10.525		10.556	18.449	33.776	
3.047				2.313	-5.975	3.546	1.572
-1.209	-21.862	-6.451		2.192	-5.105	14.449	17.259
-3.067				10.968	6.584	-2.746	14.824
5.193	43.359	19.327	36.529	32.288	42.547	5.161	4.426
1.713	6.797		18.432	10.481	11.854	12.49	22.351
4.741	29.869	2.534		20.6	20.6	-0.57	1.545
22.881	-20.416	-1.388	21.062	7.035	6.704	20.716	14.51
	-10.951	-2.215	4.545	0.551	-0.47	11.028	25.78
-16.583				-2.93	-6.291	4.529	4.529
1.189				12.306	12.306	8.805	8.805
	-34.26	-4.799		-7.713	-7.713	-5.263	3.488
	4.33	-1.37		1.02	3.781	-1.437	-4.582
19.576	8.805	10.357	6.318	8.177	9.08	2.999	29.928
				-3.799	-4.389		
				4.04	1.382	4.45	4.45
				9.983	9.983	18.667	
4.754				4.635	11.626	13.166	
9.318	1.929			3.051	3.051	8.818	3.302
	4.202	0.726	12.163	12.163	12.163	2.677	4.643
-4.448	13.035	10.505	22.732	0.956	0.956	12.776	12.047
				4.782	4.29	1.129	-0.804
-0.713				5.974	9.801	9.266	9.266

driver_loss_17q11.2	driver_loss_17q23.1	driver_loss_17q25.1	driver_loss_18q21.2	driver_loss_19p13.11	driver_loss_20p11.22	driver_tri_12	driver_gain_2p
19.314	5.583	11.505	15.025	11.505	11.476	14.394	2.499
16.389	4.23	-0.189	15.698	3.799	-2.193	5.729	-1.373
	21.586	20.93	-13.508	20.93	13.514	6.315	7.028
10.588	84.992	36.428	49.313	35.715	25.994	19.432	5.102
3.772	21.845	25.205	11.913	18.939	19.556	15.286	7.121
13.203		1.104	9.716	1.104	1.104	9.686	6.347
7.271	1.291	4.079	1.986	5.127	1.021	3.654	-2.611
19.771	3.804	1.761	6.392	1.761	2.103	5.064	5.719
7.594	25.597	4.352	11.653	4.352	4.352	17.787	5.186
13.719	40.593	48.462	-8.269	42.751	18.834	13.503	3.846
10.249		2.151	-10.678	2.151	2.151	-0.822	-5.176
9.308	46.62	47.671	-16.451	47.671	33.889	17.669	13.418
	40.075	37.817	21.208	35.012	27.427	20.352	8.456
13.669	39.185	46.073	3.906	47.317	28.978	17.251	-1.492
6.215	1.123	2.857	4.729	2.857	3.382	1.123	-0.903
26.032	0.352	1.493	3.281	11.134	0.845	9.736	-1.945
14.875	5.072	2.983	-1.25	2.983	2.983	9.235	-1.103
21.788	12.445	14.111	16.096	14.111	14.111	12.445	9.425
	15.053	38.796	15.164	38.154	13.419	18.994	9.606
	33.776	34.762	17.528	34.762	31.576	19.396	11.395
1.572	4.61	7.03	12.231	7.03	7.03	3.529	-0.113
17.259	14.193	6.061	-14.888	12.904	-9.432	13.78	-0.273
14.824	-5.15	-4.671	3.827	-4.671	-4.671	6.048	9.12
4.426	6.976	16.631	8.506	22.204	28.54	10.341	21.276
22.351	9.243	6.689	0.314	13.247	6.793	12.164	4.224
1.545	-0.57	14.956	-1.211	14.956	18.568	10.499	13.605
14.51	20.795	27.676	-8.078	37.307	5.621	7.648	16.794
25.78	-7.193	13.065	-3.717	13.065	2.622	2.064	0.424
4.529		3.978	-20.413	3.978	3.978	4.627	10.154
8.805		6.624	-8.914	6.624	6.624	13.898	2.315
3.488	-6.898	2.939	-8.169	2.939	-14.542	1.357	-7.618
-4.582	-0.308	3.883	2.546	3.883	3.883	3.808	-2.379
29.928	0.663	5.582	4.344	9.284	8.342	7.247	1.06
		-4.325	5.15	-4.325	-4.325	-3.033	2.493
4.45		18.308	13.347	18.308	18.308	4.479	10.109
	18.667	2.789	1.824	2.789	2.789	14.445	6.093
	13.166	12.201	4.315	12.201	12.201	9.849	3.718
3.302	11.736	31.224	2.055	26.596	14.206	8.004	6.199
4.643	2.105	6.622	6.655	18.989	4.883	4.664	3.961
12.047	18.515	10.479	18.105	13.625	0.998	12.698	-7.813
-0.804	3.776	5.813	-1.697	5.813	5.813	1.818	5.275
9.266		32.152	13.906	32.152	32.152	14.682	12.315

FIG. 41 (Continued)

driver_loss_11q	driver_loss_17p	driver_loss_4p	driver_loss_6q	driver_loss_8p	driver_IGLV321_R110
	13.299	13.299	12.834	-1.379	12.834
14.371	4.508	4.508	0.054	15.456	0.054
			-3.876	8.643	-3.876
10.806			-4.262	8.584	-4.262
6.727			-0.641	4.332	-0.641
			1.827	8.489	1.827
			-3.251	11.5	-3.251
2.832	-0.919	-0.919	3.723	3.436	3.723
14.899			-2.511	18.642	-2.511
			-16.171	25.162	-16.171
-1.037			-43.24	-8.803	-43.24
5.936			-41.905	9.332	-41.905
3.693			9.5	9.496	9.5
20.002			-4.88	8.788	-4.88
7.446			1.875	-8.76	1.875
			8.707	4.568	8.707
-6.14			5.011	1.085	5.011
8.194			-7.115	2.358	-7.115
7.757	14.592	14.592	8.166	2.786	8.166
7.646			-4.516	15.479	-4.516
3.047			-0.704	-7.493	-0.704
-1.209			4.999	-2.52	4.999
-3.067			-16.61	1.035	-16.61
5.193	3.454	3.454	14.42	69.153	14.42
1.713			0.853	7.597	0.853
4.741			12.062	0.282	12.062
22.881	1.336	1.336	-30.546	6.704	-30.546
			-29.324	-7.471	-29.324
-16.583			-47.982	-17.473	-47.982
1.189			35.757	12.306	35.757
			-14.386	-4.897	-14.386
			-8.132	3.247	-8.132
19.576			5.974	30.882	5.974
			-23.702	-2.523	-23.702
			-13.175	-0.852	-13.175
			2.082	0.823	2.082
4.754			-15.058	8.204	-15.058
9.318			4.954	8.86	4.954
			10.915	29.693	10.915
-4.448			-23.668	-5.863	-23.668
			6.849	-0.195	6.849
-0.713			16.708	0.763	16.708

FIG. 41 (Continued)

METHODS FOR TREATMENT SELECTION FOR CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation under 35 U.S.C. § 111(a) of PCT Application No. PCT/US2023/074708, filed Sep. 20, 2023, which claims priority to and the benefit of U.S. Provisional Patent Application No. 63/408,452, filed Sep. 20, 2022, the entire contents of each of which are incorporated by reference herein.

STATEMENT OF RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH

[0002] This invention was made with government support under Grant No. CA206978 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND OF THE INVENTION

[0003] Chronic lymphocytic leukemia (CLL) affected about 904,000 people globally in 2015 and resulted in 60,700 deaths. Despite recent advances in chronic lymphocytic leukemia (CLL) therapy, such as the use of targeted agents including Bruton's tyrosine kinase (BTK) inhibitor ibrutinib and the potent BCL-2 antagonist venetoclax, this disease remains incurable for most patients, who are refractory or become resistant to the agents. Thus, identifying new treatment regimens for CLL and building a precision medicine framework that can match CLL patients to the appropriate drugs are of high priority.

SUMMARY OF THE INVENTION

[0004] As described below, the present invention features compositions, panels of biomarkers, and methods for selecting a subject with chronic lymphocytic leukemia (CLL) for treatment using an agent and/or for inclusion in a clinical trial using the agent to treat CLL.

[0005] In one aspect, the invention features a method of treating a selected subject having chronic lymphocytic leukemia, the method comprising administering one of the following agents to the selected subject, wherein the subject is characterized as sensitive to the agent by having one of the following features:

Drug	Feature	Direction
AZD5991	EC-i	Sensitive
Azacitidine	CARD11	Sensitive
Cerdulatinib	loss__13q14.13	Sensitive
GSK690693	i-CLL	Sensitive
Rapamycin	i-CLL	Sensitive
Rapamycin	EC-m4	Sensitive
Rapamycin	M-CLL	Sensitive
Umbralisib	M-CLL	Sensitive
Trametinib	CHD2	Sensitive
Bendamustine	loss__12p13.31a	Sensitive
Bendamustine	loss__5p15.33	Sensitive
Bendamustine	loss__7p22.2	Sensitive
Bendamustine	loss__14q32.12	Sensitive
Cerdulatinib	loss__13q14.3	Sensitive
Cerdulatinib	loss__13q14.13	Sensitive

-continued

Drug	Feature	Direction
JQ1	FBXW7	Sensitive
Navitoclax	M-CLL	Sensitive
Rapamycin	M-CLL	Sensitive
Ruxolitinib	loss__13q14.3	Sensitive
Venetoclax	loss__13q14.3	Sensitive
AZD5991	loss__3p13	Sensitive
Cerdulatinib	loss__13q14.3	Sensitive
Cerdulatinib	loss__13q14.13	Sensitive
Entospletinib	tri__12	Sensitive
GSK690693	i-CLL	Sensitive
JQ1	EC-i	Sensitive
Selinexor	MYD88	Sensitive
Trametinib	CHD2	Sensitive
Vorinostat	EC-m2	Sensitive
AZD5991	EC-i	Sensitive
Azacitidine	CARD11	Sensitive
Cerdulatinib	loss__13q14.13	Sensitive
GSK690693	i-CLL	Sensitive
Rapamycin	i-CLL	Sensitive
Rapamycin	EC-m4	Sensitive
Rapamycin	M-CLL	Sensitive
Umbralisib	M-CLL	Sensitive
Trametinib	CHD2	Sensitive
Bendamustine	loss__12p13.31a	Sensitive
Bendamustine	loss__5p15.33	Sensitive
Bendamustine	loss__7p22.2	Sensitive
Bendamustine	loss__14q32.12	Sensitive
Cerdulatinib	loss__13q14.3	Sensitive
Cerdulatinib	loss__13q14.13	Sensitive
JQ1	FBXW7	Sensitive
Navitoclax	M-CLL	Sensitive
Rapamycin	M-CLL	Sensitive
Ruxolitinib	loss__13q14.3	Sensitive
Venetoclax	loss__13q14.3	Sensitive
AZD5991	loss__3p13	Sensitive
Cerdulatinib	loss__13q14.3	Sensitive
Cerdulatinib	loss__13q14.13	Sensitive
Entospletinib	tri__12	Sensitive
GSK690693	i-CLL	Sensitive
JQ1	EC-i	Sensitive
Selinexor	MYD88	Sensitive
Trametinib	CHD2	Sensitive
Vorinostat	EC-m2	Sensitive
AZD5991	EC-i	Sensitive
Azacitidine	CARD11	Sensitive
Cerdulatinib	loss__13q14.13	Sensitive
GSK690693	i-CLL	Sensitive
Rapamycin	i-CLL	Sensitive
Rapamycin	EC-m4	Sensitive
Rapamycin	M-CLL	Sensitive
Umbralisib	M-CLL	Sensitive
Trametinib	CHD2	Sensitive
Bendamustine	loss__12p13.31a	Sensitive
Bendamustine	loss__5p15.33	Sensitive
Bendamustine	loss__7p22.2	Sensitive
Bendamustine	loss__14q32.12	Sensitive
Cerdulatinib	loss__13q14.3	Sensitive
Cerdulatinib	loss__13q14.13	Sensitive
JQ1	FBXW7	Sensitive
Navitoclax	M-CLL	Sensitive
Rapamycin	M-CLL	Sensitive
Ruxolitinib	loss__13q14.3	Sensitive
Venetoclax	loss__13q14.3	Sensitive
AZD5991	loss__3p13	Sensitive
Cerdulatinib	loss__13q14.3	Sensitive
Cerdulatinib	loss__13q14.13	Sensitive
Entospletinib	tri__12	Sensitive
GSK690693	i-CLL	Sensitive
JQ1	EC-i	Sensitive
Selinexor	MYD88	Sensitive
Trametinib	CHD2	Sensitive
Vorinostat	EC-m2	Sensitive

[0006] In another aspect, the invention features a method of treating a subject having chronic lymphocytic leukemia,

the method comprising administering an agent to a sensitive subject, wherein the subject's sensitivity is determined by identifying the presence of a feature from among the following expression subtypes, drives, genetic alterations, or CLL subtypes, or electing not to administer an agent to a resistant subject wherein the subject's resistance is determined by identifying the presence of a feature from among the following expression subtypes, drives, genetic alterations, or CLL subtypes, wherein the agent, feature, and sensitivity or resistance is as follows:

Agent	Feature	Direction
A-1331852	EC-m2	Resistant
AZD5991	EC-i	Sensitive
Azacitidine	CARD11	Sensitive
Cerdulatinib	loss__13q14.13	Sensitive
GSK690693	i-CLL	Sensitive
Gandotinib	EC-i	Resistant
Navitoclax	EC-m2	Resistant
Nutlin-3	priortrt__Post	Resistant
Nutlin-3	FBXW7	Resistant
Rapamycin	EC-ul	Resistant
Rapamycin	i-CLL	Sensitive
Rapamycin	U-CLL	Resistant
Rapamycin	EC-m4	Sensitive
Rapamycin	n-CLL	Resistant
Rapamycin	M-CLL	Sensitive
Umbralisib	U-CLL	Resistant
Umbralisib	n-CLL	Resistant
Umbralisib	M-CLL	Sensitive
Venetoclax	EC-m2	Resistant
Rapamycin	n-CLL	Resistant
Trametinib	CHD2	Sensitive
Bendamustine	loss__12p13.31a	Sensitive
Bendamustine	loss__5p15.33	Sensitive
Bendamustine	loss__7p22.2	Sensitive
Bendamustine	loss__14q32.12	Sensitive
Cerdulatinib	loss__13q14.3	Sensitive
Cerdulatinib	loss__13q14.13	Sensitive
Gandotinib	EC-i	Resistant
JQ1	FBXW7	Sensitive
MK-2206	priortrt__Post	Resistant
Navitoclax	U-CLL	Resistant
Navitoclax	n-CLL	Resistant
Navitoclax	M-CLL	Sensitive
Nutlin-3	priortrt__Post	Resistant
Rapamycin	U-CLL	Resistant
Rapamycin	M-CLL	Sensitive
Ruxolitinib	loss__13q14.3	Sensitive
Venetoclax	loss__13q14.3	Sensitive
AZD5991	loss__3p13	Sensitive
Cerdulatinib	loss__13q14.3	Sensitive
Cerdulatinib	loss__13q14.13	Sensitive
Entospletinib	tri__12	Sensitive
GSK690693	i-CLL	Sensitive
JQ1	EC-i	Sensitive
Rapamycin	n-CLL	Resistant
Selinexor	MYD88	Sensitive
Trametinib	CHD2	Sensitive
Vorinostat	EC-m4	Resistant
Vorinostat	EC-m2	Sensitive
A-1331852	EC-m2	Resistant
AZD5991	EC-i	Sensitive
Azacitidine	CARD11	Sensitive
Cerdulatinib	loss__13q14.13	Sensitive
GSK690693	i-CLL	Sensitive
Gandotinib	EC-i	Resistant
Navitoclax	EC-m2	Resistant
Nutlin-3	priortrt__Post	Resistant
Nutlin-3	FBXW7	Resistant
Rapamycin	EC-ul	Resistant
Rapamycin	i-CLL	Sensitive
Rapamycin	U-CLL	Resistant
Rapamycin	EC-m4	Sensitive

-continued

Agent	Feature	Direction
Rapamycin	n-CLL	Resistant
Rapamycin	M-CLL	Sensitive
Umbralisib	U-CLL	Resistant
Umbralisib	n-CLL	Resistant
Umbralisib	M-CLL	Sensitive
Venetoclax	EC-m2	Resistant
Rapamycin	n-CLL	Resistant
Trametinib	CHD2	Sensitive
Bendamustine	loss__12p13.31a	Sensitive
Bendamustine	loss__5p15.33	Sensitive
Bendamustine	loss__7p22.2	Sensitive
Bendamustine	loss__14q32.12	Sensitive
Cerdulatinib	loss__13q14.3	Sensitive
Cerdulatinib	loss__13q14.13	Sensitive
Gandotinib	EC-i	Resistant
JQ1	FBXW7	Sensitive
MK-2206	priortrt__Post	Resistant
Navitoclax	U-CLL	Resistant
Navitoclax	n-CLL	Resistant
Navitoclax	M-CLL	Sensitive
Nutlin-3	priortrt__Post	Resistant
Rapamycin	U-CLL	Resistant
Rapamycin	M-CLL	Sensitive
Ruxolitinib	loss__13q14.3	Sensitive
Venetoclax	loss__13q14.3	Sensitive
AZD5991	loss__3p13	Sensitive
Cerdulatinib	loss__13q14.3	Sensitive
Cerdulatinib	loss__13q14.13	Sensitive
Entospletinib	tri__12	Sensitive
GSK690693	i-CLL	Sensitive
JQ1	EC-i	Sensitive
Rapamycin	n-CLL	Resistant
Selinexor	MYD88	Sensitive
Trametinib	CHD2	Sensitive
Vorinostat	EC-m4	Resistant
Vorinostat	EC-m2	Sensitive
A-1331852	EC-m2	Resistant
AZD5991	EC-i	Sensitive
Azacitidine	CARD11	Sensitive
Cerdulatinib	loss__13q14.13	Sensitive
GSK690693	i-CLL	Sensitive
Gandotinib	EC-i	Resistant
Navitoclax	EC-m2	Resistant
Nutlin-3	priortrt__Post	Resistant
Nutlin-3	FBXW7	Resistant
Rapamycin	EC-ul	Resistant
Rapamycin	i-CLL	Sensitive
Rapamycin	U-CLL	Resistant
Rapamycin	EC-m4	Sensitive
Rapamycin	n-CLL	Resistant
Rapamycin	M-CLL	Sensitive
Umbralisib	U-CLL	Resistant
Umbralisib	n-CLL	Resistant
Umbralisib	M-CLL	Sensitive
Venetoclax	EC-m2	Resistant
Rapamycin	n-CLL	Resistant
Trametinib	CHD2	Sensitive
Bendamustine	loss__12p13.31a	Sensitive
Bendamustine	loss__5p15.33	Sensitive
Bendamustine	loss__7p22.2	Sensitive
Bendamustine	loss__14q32.12	Sensitive
Cerdulatinib	loss__13q14.3	Sensitive
Cerdulatinib	loss__13q14.13	Sensitive
Gandotinib	EC-i	Resistant
JQ1	FBXW7	Sensitive
MK-2206	priortrt__Post	Resistant
Navitoclax	U-CLL	Resistant
Navitoclax	n-CLL	Resistant
Navitoclax	M-CLL	Sensitive
Nutlin-3	priortrt__Post	Resistant
Rapamycin	U-CLL	Resistant
Rapamycin	M-CLL	Sensitive
Ruxolitinib	loss__13q14.3	Sensitive
Venetoclax	loss__13q14.3	Sensitive

-continued

Agent	Feature	Direction
AZD5991	loss_3p13	Sensitive
Cerdulatinib	loss_13q14.3	Sensitive
Cerdulatinib	loss_13q14.13	Sensitive
Entospletinib	tri_12	Sensitive
GSK690693	i-CLL	Sensitive
JQ1	EC-i	Sensitive
Rapamycin	n-CLL	Resistant
Selinexor	MYD88	Sensitive
Trametinib	CHD2	Sensitive
Vorinostat	EC-m4	Resistant
Vorinostat	EC-m2	Sensitive

(e.g., AZD5991 is administered to a subject identified as sensitive by detecting characteristics of Ec-i in a biological sample of the subject).

[0007] In another aspect, the invention features a method of treating a chronic lymphocytic leukemia (CLL) EC-i expression subtype in a subject, the method involves administering to the subject navitoclax.

[0008] In another aspect, the invention features a method of treating a chronic lymphocytic leukemia (CLL) EC-m1 expression subtype in a subject, the method involves administering to the subject nutlin-3, navitoclax, or cerdulatinib.

[0009] In another aspect, the invention features a method of treating a chronic lymphocytic leukemia (CLL) EC-m2 expression subtype in a subject, the method involves administering to the subject abexinostat, duvelisib, idelalisib, entospletinib, or vorinostat.

[0010] In another aspect, the invention features a method of treating a chronic lymphocytic leukemia (CLL) EC-m3 expression subtype in a subject, the method involves administering to the subject venetoclax, navitoclax, or Abexinostat.

[0011] In another aspect, the invention features a method of treating a chronic lymphocytic leukemia (CLL) EC-m4 expression subtype in a subject, the method involves administering to the subject navitoclax, nutlin-3, or gandotinib.

[0012] In another aspect, the invention features a method of treating a chronic lymphocytic leukemia (CLL) EC-o expression subtype in a subject, the method involves administering to the subject gandotinib, abexinostat, or cerdulatinib.

[0013] In another aspect, the invention features a method of treating a chronic lymphocytic leukemia (CLL) EC-ul expression subtype in a subject, the method involves administering to the subject gandotinib.

[0014] In another aspect, the invention features a method of treating a chronic lymphocytic leukemia (CLL) EC-u2 expression subtype in a subject, the method involves administering to the subject ibrutinib, A-1331852, navitoclax, or rapamycin.

[0015] In another aspect, the invention features a method of treating a chronic lymphocytic leukemia (CLL) M-CLL subtype in a subject, the method involves administering to the subject navitoclax or abexinostat.

[0016] In another aspect, the invention features a method of treating a chronic lymphocytic leukemia (CLL) U-CLL subtype in a subject, the method involves administering to the subject A-1331852, atorvastatin, AZD5991, bendamustine, onalespib, trametinib, voruciclib, or zanubrutinib.

[0017] In another aspect, the invention features a method of treating a chronic lymphocytic leukemia (CLL) in a subject, the method involves administering to the subject:

[0018] (a) venetoclax and an MCL1 inhibitor selected from the group consisting of AZD5991, tapotoclax, MIK665, A-1210477, ANJ810, PRT1419, AS00491, APG-3526, CT-03, and CPT-628; or

[0019] (b) ibrutinib and a BCL2 inhibitor selected from the group consisting of venetoclax, ZN-d5, lisaftoclax, S55746, and AZD4320.

[0020] In another aspect, the invention features a method of treating a chronic lymphocytic leukemia (CLL) in a selected subject, the method involves administering to the subject an agent with a delta priming value listed in FIG. **14** greater than 15 associated with a driving alteration, wherein the subject is selected as having a neoplasia containing the driving alteration, wherein the driving alteration is:

[0021] (a) in a gene encoding a polypeptide selected from the group consisting of ATM, CARD11, CHD2, FBXW7, ITIH2, NOTCH1, NRAS, POTI, SF3B1, TP53, and ZMYM3; or

[0022] (b) in a genomic region selected from the group consisting of 7922.1, 15q24.2, 16p11.2, 19pl3.3, 1921.3, 1942.13, 2p11.2, 2q31.1, 3p21.31, 3p13, 5pl5.33, 7p22.2, 9q34.3, 1Opl2.2, 10q24.2, 10q24.32, 11q22.3, 12pl3.31a, 13q14.13, 13q14.3, 14q32.12, 16q22.1, 17pl3.3, 17p13.1, and chromosome 12, and/or 2p.

[0023] In another aspect, the invention features a method for treating a selected subject having chronic lymphocytic leukemia (CLL), the method involves:

[0024] (a) characterizing the CLL as having:

[0025] i. a mutated (M-CLL) or unmutated IGHV (U-CLL) subtype;

[0026] ii. an expression subtype selected from EC-i, EC-m1, EC-m2, EC-m3, EC-m4, EC-o, EC-ul, or EC-u2; and/or

[0027] iii. a driving alteration in a gene encoding a polypeptide selected from the group consisting of ATM, CARD11, CHD2, FBXW7, ITIH2, NOTCHI, NRAS, POTI, SF3B1, TP53, and ZMYM3; and/or

[0028] iv. a driving alteration in a genomic region selected from the group consisting of 7q22.1, 15q24.2, 16pl1.2, 19pl3.3, 1921.3, 1942.13, 2p11.2, 2q31.1, 3p21.31, 3p13, 5pl5.33, 7p22.2, 9q34.3, 1Opl2.2, 10q24.2, 10q24.32, 11q22.3, 12p13.31a, 13q14.13, 13q14.3, 14q32.12, 16q22.1, 17pl3.3, 17p13.1, chromosome 12, and 2p; and

[0029] (b) administering an agent to the selected subject, wherein the agent has a delta priming value listed in FIG. **14** greater than 15 associated with the CLL subtype or driving alteration.

[0030] In another aspect, the invention features a method for selecting a subject having chronic lymphocytic leukemia (CLL) for inclusion in or exclusion from a clinical trial to study an agent for treatment of CLL, the method involves:

[0031] (a) characterizing the CLL as having:

[0032] i. a mutated (M-CLL) or unmutated IGHV (U-CLL) subtype;

[0033] ii. an expression subtype selected from EC-i, EC-m1, EC-m2, EC-m3, EC-m4, EC-o, EC-ul, or EC-u2; and/or

[0034] iii. a driving alteration in a gene encoding a polypeptide selected from the group consisting of

ATM, CARD11, CHD2, FBXW7, ITIH2, NOTCHI, NRAS, POT1, SF3B1, TP53, and ZMYM3; and/or

[0035] iv. a driving alteration in a genomic region selected from the group consisting of 7q22.1, 15q24.2, 16p11.2, 19pl3.3, 1921.3, 1942.13, 2p11.2, 2q31.1, 3p21.31, 3p13, 5p15.33, 7p22.2, 9q34.3, 1Op12.2, 10q24.2, 10q24.32, 11q22.3, 12p13.31a, 13q14.13, 13q14.3, 14q32.12, 16q22.1, 17pl3.3, 17pl3.1, chromosome 12, and 2p; and

[0036] (b) selecting the subject for inclusion in the clinical trial if the agent has a positive delta priming value of greater than 15 listed in FIG. **14** for the subtype and/or driving alteration of the CLL, and otherwise excluding the subject from the clinical trial.

[0037] The method of the previous aspects, wherein the driving alteration to the genomic region is a duplication or a deletion.

[0038] In another aspect, the invention features a combination therapeutic containing venetoclax and one or more of the following: abexinostat, navitoclax, cerdulatinib, AZD5991, atorvastatin, zanubrutinib, GSK690693, trametinib, ponatinib, bendamustine, nutlin-3, and rapamycin.

[0039] In another aspect, the invention features a combination therapeutic containing venetoclax and one or more of the following: abexinostat, navitoclax, cerdulatinib, AZD5991, atorvastatin, zanubrutinib, GSK690693, trametinib, ponatinib, bendamustine, nutlin-3, and rapamycin.

[0040] In another aspect, the invention features a combination therapeutic containing venetoclax and one or more of the following: abexinostat, navitoclax, cerdulatinib, AZD5991, atorvastatin, 30 zanubrutinib, GSK690693, trametinib, ponatinib, bendamustine, nutlin-3, and rapamycin.

[0041] In another aspect, the invention features a combination therapeutic containing venetoclax and one or more of the following: navitoclax, abexinostat, dasatinib, idelaslisib, duvelisib, cerdulatinib, bendamustine, GSK690693, nirogacestat, trametinib, and rapamycin.

[0042] In another aspect, the invention features a combination therapeutic containing venetoclax and an MCL1 inhibitor.

[0043] In another aspect, the invention features a combination therapeutic containing venetoclax and one or more of the following: abexinostat, navitoclax, cerdulatinib, AZD5991, atorvastatin, 5 zanubrutinib, GSK690693, trametinib, ponatinib, bendamustine, nutlin-3, and rapamycin. In various embodiments, the two agents are formulated separately. In various embodiments, the two agents are administered concurrently or sequentially within at least about 1, 3, 6, 9, 12, or 24 hours of one another. In various embodiments, the two agents are administered within 3, 5, 7, 10, 14, 21, or 28 days of one another.

[0044] In another aspect, the invention features a method of treating a chronic lymphocytic leukemia (CLL) in a subject, the method comprising administering to the subject A-1331852, AZD5991, azacitidine, cerdulatinib, GSK690693, umbralisib, trametinib, bendamustine, cerdulatinib, gandotinib, JQ1, MK-2206, navitoclax, nutlin-3, ruxolitinib, venetoclax, AZD5991, cerdulatinib, entospletinib, GSK690693, JQ1, rapamycin, selinexor, tgrametinib, or vorinostat.

[0045] In various embodiments of any previous aspect, Ec-i comprises an increase in GRIK3, IQGAP2, FCER1G, STK32B, GADD45A, ITGAX, KLF3, RFTN1, PTK2, DFNB31, and ZMAT1 polypeptides, or nucleic acid molecules encoding said polypeptide;

[0046] wherein EC-m1 comprises an increase in one or more of TFEC, COL18A1, SLC19A1, NRIP1, KCNH2, P2RX1, ARRDC5, BEX4, and APP polypeptides, or nucleic acid molecules encoding said polypeptide;

[0047] wherein EC-m2 comprises an increase in one or more of EML6, HCK, CD1C, VPS37B, CYBB, NXPH4, BTNL9, KLRK1, IQSEC1, BANKI, LEF1, SH3D21, FMOD, SEMA4A, CTLA4, ADTRP, IGSF3, IGFBP4, PDGFD, and APOD polypeptides, or nucleic acid molecules encoding said polypeptide;

[0048] wherein EC-m3 comprises an increase in one or more of MS4A4E, MYL9, NT5E, MS4A6A, PITPNC1, CNTNAP2, IGF2BP3, WNT3, CLDN7, TCF7, BASP1, FLJ20373, MAP4K4, LRRK2, SAMSN1, CEACAMI, TNFRSF13B, PHF16, MID1IPI, and ABCA9 polypeptides or nucleic acid molecules encoding said polypeptide;

[0049] wherein EC-m4 comprises an increase in one or more of MYBL1, NUGGC, GNG8, AEBP1, HIP1R, LATS2, RIMKLB, EML6, FADS3, MBOAT1, LCN10, DCLK2, and GLUL polypeptides or nucleic acid molecules encoding said polypeptide;

[0050] wherein EC-o comprises an increase in one or more of ACSM3, TOX2, PHF16, SESN3, TBC1D9, PIP5K1B, SIK1, DUSP5, GNG7, HIVEP3, MARCKSL1, GPR183, HRK, and PITPNC1 polypeptides, or nucleic acid molecules encoding said polypeptide;

[0051] wherein EC-ul comprises an increase in one or more of SEPT10, LDOC1, LPL, KANK2, SOWAHC, DUSP26, OSBPL5, WNT9A, FGFR1, GTSF1L, ADD3, AKT3, COBLL1, MNDA, FCRL3, FAM49A, FCRL2, SLC2A3, and MARCKS polypeptides, or nucleic acid molecules encoding said polypeptide; or

[0052] wherein EC-u2 comprises an increase in one or more of ITGB5, BCL7A, PPP1R9A, TSPAN13, SLC12A7, SSBP3, VASH1, SPG20, IL13RA1, NR3C2, TUBG2, ZNF804A, and IL2RA polypeptides, or nucleic acid molecules encoding said polypeptide.

[0053] In various embodiments of any previous aspect, levels of the polypeptide or polypeptide are increased.

[0054] In various embodiments of any previous aspect, M-CLL is treated with navitoclax, nutlin-3, duvelisib, ibrutinib, or venetoclax.

[0055] In various embodiments of any previous aspect, U-CLL is treated with navitoclax, nutlin-3, duvelisib, ibrutinib, dasatinib, venetoclax, or idelasib.

[0056] In various embodiments of any previous aspect, venetoclax is administered in combination with an MCL1 inhibitor.

[0057] In various embodiments of any previous aspect, a subject having CLL characterized as EC-m3, or having a gain of function in 16p11.2, or a loss of function in 13a14.3 is administered venetoclax in combination with an MCL1 inhibitor.

[0058] In various embodiments of any previous aspect, a subject having a CLL characterized as 20 having a trisomy-12 driver is administered zanubrutinib or acalabrutinib.

[0059] In various embodiments of any previous aspect, a subject having CLL characterized as EC-m2, M-CLL, and/or having a trisomy-12 driver is administered zanubrutinib.

[0060] In various embodiments of any previous aspect, a subject having a CLL characterized as EC-i is administered abexinostat.

[0061] In various embodiments of any previous aspect, a subject receiving venetoclax is administered one or more of the following: abexinostat, navitoclax, cerdulatinib, AZD5991, atorvastatin, zanubrutinib, GSK690693, trametinib, ponatinib, bendamustine, nutlin-3, and rapamycin.

[0062] In various embodiments of any previous aspect, a subject receiving venetoclax is administered one or more of the following: abexinostat, navitoclax, cerdulatinib, AZD5991, atorvastatin, zanubrutinib, GSK690693, trametinib, ponatinib, bendamustine, nutlin-3, and rapamycin.

[0063] In various embodiments of any previous aspect, a subject receiving venetoclax is administered one or more of the following: abexinostat, navitoclax, cerdulatinib, AZD5991, atorvastatin, zanubrutinib, GSK690693, trametinib, ponatinib, bendamustine, nutlin-3, and rapamycin.

[0064] In various embodiments of any previous aspect, a subject receiving venetoclax is administered one or more of the following: navitoclax, abexinostat, dasatinib, idelaslisib, 5 duvelisib, cerdulatinib, bendamustine, GSK690693, nirogacestat, trametinib, and rapamycin.

[0065] In various embodiments of any previous aspect, venetoclax is administered in combination with an MCL1 inhibitor.

[0066] In various embodiments of any previous aspect, a subject receiving venetoclax is administered one or more of the following: abexinostat, navitoclax, cerdulatinib, AZD5991, atorvastatin, zanubrutinib, GSK690693, trametinib, ponatinib, bendamustine, nutlin-3, and rapamycin.

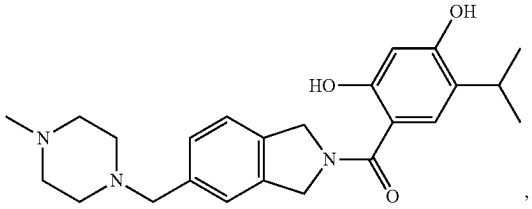
[0067] Compositions and articles defined by the invention were isolated or otherwise manufactured in connection with the examples provided below. Other features and advantages of the invention will be apparent from the detailed description, and from the claims.

Definitions

[0068] Unless defined otherwise, all technical and scientific terms used herein have the meaning commonly understood by a person skilled in the art to which this invention belongs. The following references provide one of skill with a general definition of many of the terms used in this invention: Singleton et al., Dictionary of Microbiology and Molecular Biology (2nd ed. 1994); The Cambridge Dictionary of Science and Technology (Walker ed., 1988); The Glossary of Genetics, 5th Ed., R. Rieger et al. (eds.), Springer Verlag (1991); and Hale & Marham, The Harper Collins Dictionary of Biology (1991). As used herein, the following terms have the meanings ascribed to them below, unless specified otherwise.

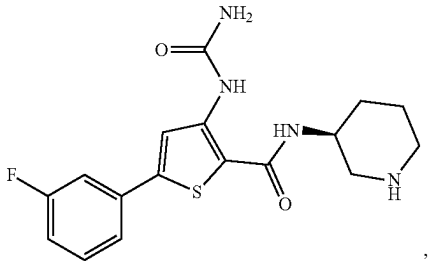
[0069] The terms "biomarker" and "marker" are used interchangeably herein to refer to a protein, nucleic acid molecule, clinical indicator, or other analyte that is associated with a disease. In one embodiment, a marker of chronic lymphocytic leukemia (CLL) is differentially present in a biological sample obtained from a subject having or at risk of developing chronic lymphocytic leukemia (CLL) relative to a reference. A marker is differentially present if the mean or median level of the biomarker present in the sample is statistically different from the level present in a reference. A reference level may be, for example, the level present in a sample obtained from a healthy control subject or the level obtained from the subject at an earlier timepoint, i.e., prior to treatment. Common tests for statistical significance include, among others, t-test, ANOVA, Kruskal-Wallis, Wilcoxon, Mann-Whitney and odds ratio. Biomarkers, alone or in combination, provide measures of relative likelihood that a subject belongs to a phenotypic status of interest. Biomarkers can be used to classify a chronic lymphocytic leukemia (CLL). The differential presence of a marker of the invention in a subject sample can be useful in characterizing the subject as having or at risk of developing chronic lymphocytic leukemia (CLL), for determining the prognosis of the subject, for evaluating therapeutic efficacy, or for selecting a treatment regimen (e.g., selecting that the subject be evaluated and/or treated by a surgeon who specializes in chronic lymphocytic leukemia (CLL)). The invention includes markers that share at least about 85%, 90%, 95% or even 99% to a polypeptide sequence corresponding to a biomarker listed in Table 3A or Table 4. The invention includes markers that share at least about 85%, 90%, 95% or even 99% to a polynucleotide sequence corresponding to a gene listed in Table 3A or Table 4.

[0070] By "AT13387" is meant a chemical corresponding to CAS No. 912999-49-6, having the chemical structure



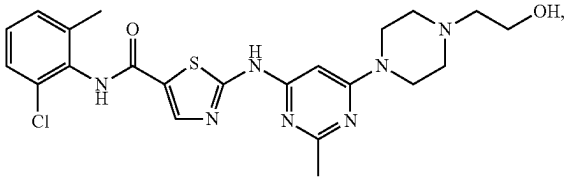
and pharmaceutically acceptable salts thereof.

[0071] By "AZD7762" is meant a chemical corresponding to CAS No. 860352-01-8, having the chemical structure



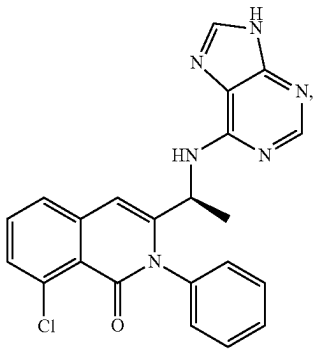
and pharmaceutically acceptable salts thereof.

[0072] By "dasatinib" is meant a chemical corresponding to CAS No. 302962-49-8, having the chemical structure



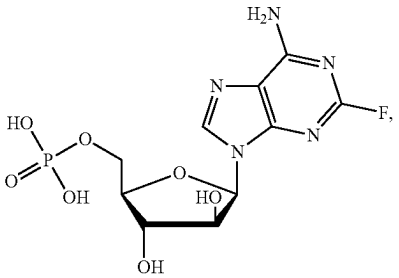
and pharmaceutically acceptable salts thereof.

[0073] By "duvelisib" is meant a chemical corresponding to CAS No. 1201438-56-3, having the chemical structure



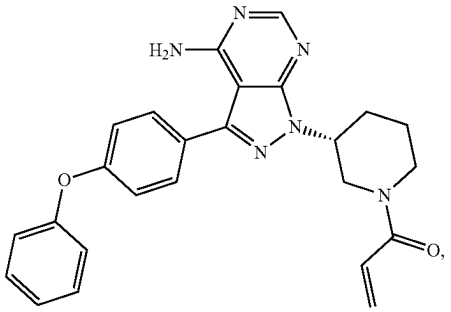
and pharmaceutically acceptable salts thereof.

[0074] By "fludarabine" is meant a chemical corresponding to CAS No. 21679-14-1, having the chemical structure



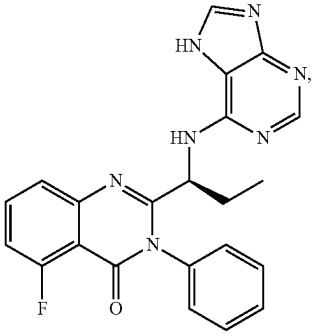
and pharmaceutically acceptable salts thereof.

[0075] By "ibrutinib" is meant a chemical corresponding to CAS No. 936563-96-1, having the chemical structure



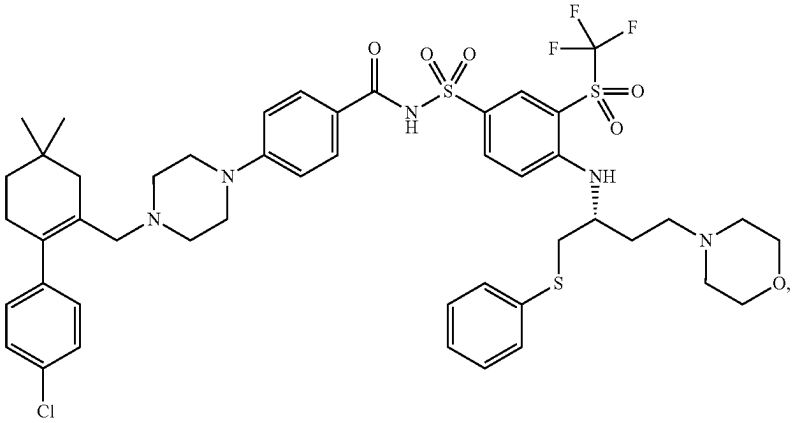
and pharmaceutically acceptable salts thereof.

[0076] By "idelalisib" is meant a chemical corresponding to CAS No. 870281-82-6, having the chemical structure



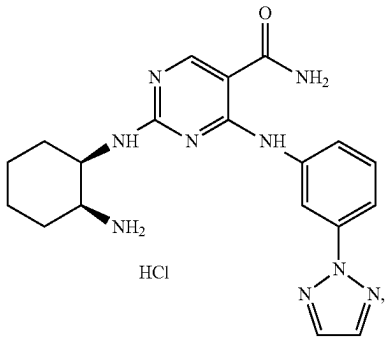
and pharmaceutically acceptable salts thereof.

[0077] By "navitoclax" is meant a chemical corresponding to CAS No. 923564-51-6, having the chemical structure



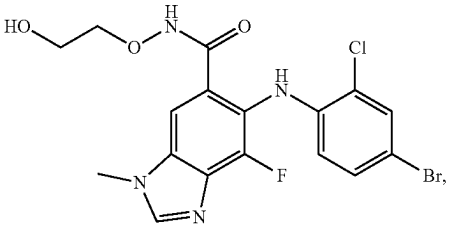
and pharmaceutically acceptable salts thereof.

[0078] By "PRT062607 HCL" is meant a chemical corresponding to CAS No. 1370261-97-4, having the chemical structure



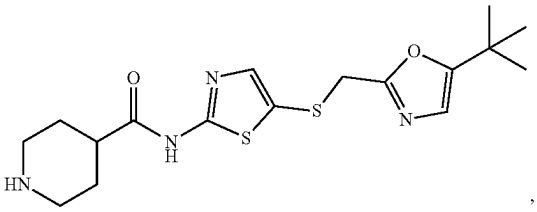
and pharmaceutically acceptable salts thereof.

[0079] By "selumetinib" is meant a chemical corresponding to CAS No. 606143-52-6, having the chemical structure



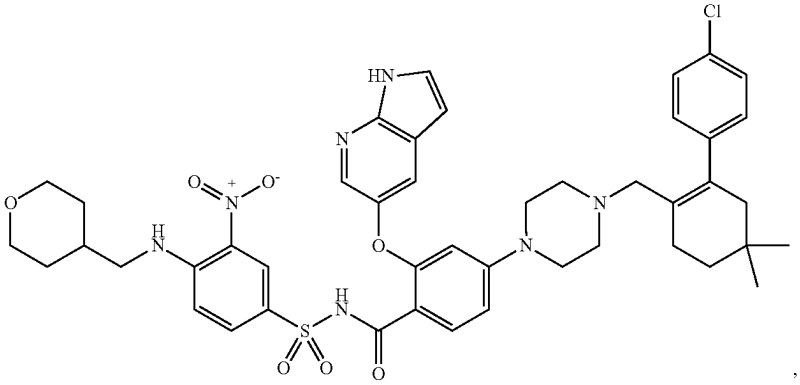
and pharmaceutically acceptable salts thereof.

[0080] By "SNS-032" is meant a chemical corresponding to CAS No. 345627-80-7, having the chemical structure



and pharmaceutically acceptable salts thereof.

[0081] By "venetoclax" is meant a chemical corresponding to CAS No. 1257044-40-8, having the chemical structure



and pharmaceutically acceptable salts thereof.

[0082] By "agent" is meant any small molecule chemical compound, antibody, nucleic acid molecule, or polypeptide, or fragments thereof.

[0083] By "ameliorate" is meant to decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease.

[0084] By "alteration" or "change" is meant an increase or decrease. An alteration may be by as little as 1%, 2%, 3%, 4%, 5%, 10%, 20%, 30%, or by 40%, 50%, 60%, or even by as much as 70%, 75%, 80%, 90%, or 100%.

[0085] By "analog" is meant a molecule that is not identical but has analogous functional or structural features. For example, a polypeptide analog retains the biological activity of a corresponding naturally-occurring polypeptide, while having certain biochemical modifications that enhance the analog's function relative to a naturally occurring polypeptide. Such biochemical modifications could increase the analog's protease resistance, membrane permeability, or half-life, without altering, for example, ligand binding. An analog may include an unnatural amino acid.

[0086] By "biological sample" is meant any tissue, cell, fluid, or other material derived from an organism. Non-limiting examples of biological samples include a bodily fluid (such as blood, blood serum, plasma, saliva, urine, ascites, cyst fluid, and the like); a homogenized tissue sample (e.g., a tissue sample obtained by biopsy); and a cell isolated from a patient sample.

[0087] By "capture molecule" or "capture reagent" is meant a reagent that specifically binds a nucleic acid molecule or polypeptide to label, select, or isolate the nucleic acid molecule or polypeptide. Non-limiting examples of capture molecules include polynucleotide probes, antibodies, and fragments thereof.

[0088] By "Chronic Lymphocytic Leukemia (CLL)" is meant a B cell neoplasm. In embodiments, CLL is diagnosed using:

[0089] Blood tests: These tests show the extent of cancer and any signs of infection. Blood tests measure levels of white and red blood cells, the amount of inflammation in the body, and liver and kidney function. A blood test can also look for genetic changes.

[0090] Bone marrow biopsy and aspiration: Doctors use these tests to look for leukemia cells in the bone marrow. They use thin, hollow needles to remove small samples of bone marrow and bone tissue for analysis.

[0091] Lymph node biopsy: A doctor may remove part or all of a lymph node (gland that helps your body fight infection) to examine it for signs of cancer.

[0092] Genetic testing: Doctors may use bone marrow samples to look for genetic changes that can lead to CLL. Genetic information can help guide treatment as described herein below.

[0093] Imaging: Doctors may use these tests, which produce detailed images of the body, to check for signs of cancer in other parts of the body. Imaging tests may include CT scan or ultrasound. In embodiments, CLL is characterized using features described herein.

[0094] As used herein, the terms "determining", "assessing", "assaying", "measuring" and "detecting" refer to both quantitative and qualitative determinations, and as such, the term "determining" is used interchangeably herein with "assaying," "measuring," and the like.

[0095] In this disclosure, "comprises," "comprising," "containing" and "having" and the like can have the meaning ascribed to them in U.S. Patent law and can mean "includes," "including," and the like; "consisting essentially of" or "consists essentially" likewise has the meaning ascribed in U.S. Patent law and the term is open-ended, allowing for the presence of more than that which is recited so long as basic or novel characteristics of that which is recited is not changed by the presence of more than that which is recited, but excludes prior art embodiments. Any embodiments specified as "comprising" a particular component(s) or element(s) are also contemplated as "consisting of" or "consisting essentially of" the particular component (s) or element(s) in some embodiments.

[0096] By "delta priming" is meant the difference in priming of a cell for apoptosis measured in the presence of an agent for treating chronic lymphocytic leukemia relative to priming of the cell in the presence of an inert carrier. In embodiments, the inert carrier is DMSO.

[0097] "Detect" refers to identifying the presence, absence or amount of the analyte to be detected.

[0098] By "driver alteration" is meant a genomic alteration that is associated with an increase in cell proliferation relative to an unaltered cell. Non-limiting examples of genes that can comprise driver alterations include ATM, CARD11, CHD2, FBXW7, ITIH2, NOTCH1, NRAS, POT1, SF3B1, TP53, and ZMYM3. Non-limiting examples of genomic region alterations that can be driver alterations include a duplication of 7q22.1, duplication of 15q24.2, duplication of 16p11.2, duplication of 19p13.3, deletion of 1q21.3, deletion of 1q42.13, deletion of 2p11.2, deletion of 2q31.1, deletion of 3p21.31, deletion of 3p13, deletion of 5p15.33, deletion of 7p22.2, deletion of 9q34.3, deletion of 10p12.2, deletion of 10q24.2, deletion of 10q24.32, deletion of 11q22.3, deletion of 12p13.31a, deletion of 13q14.13, deletion of 13q14.3, deletion of 14q32.12, deletion of 16q22.1, deletion of 17pl3.3, deletion of 17pl3.1, tri_12, and/or duplication of 2p.

[0099] By "molecular identifier" is meant an agent that when linked to a molecule of interest renders the latter detectable, via spectroscopic, photochemical, biochemical, immunochemical, or chemical means. For example, useful labels include radioactive isotopes, magnetic beads, metallic beads, colloidal particles, fluorescent dyes, electron-dense reagents, enzymes (for example, as commonly used in an ELISA), biotin, digoxigenin, or haptens.

[0100] By "disease" is meant any condition or disorder that damages or interferes with the normal function of a cell, tissue, or organ. Examples of diseases include chronic lymphocytic leukemia (CLL) and the like.

[0101] By "effective amount" is meant the amount of an agent required to ameliorate the symptoms of a disease relative to an untreated patient. The effective amount of active compound(s) used to practice the present invention for therapeutic treatment of a disease varies depending upon the manner of administration, the age, body weight, and general health of the subject. Ultimately, the attending physician or veterinarian will decide the appropriate amount and dosage regimen. Such amount is referred to as an "effective" amount.

[0102] The term "expression cluster (EC)" describes a set of genes that are co-expressed and exhibit coordinated behavior. See, for example, Abu-Jamous, B., Kelly, S. Clust: automatic extraction of optimal co-expressed gene clusters from gene expression data. Genome Biol 19, 172 (2018). https://doi.org/10.1186/s13059-018-1536-8. Expression clusters can be used to characterize disease subtypes. Expression clusters used to characterize chronic lymphocytic leukemia include the following: Ec-i, EC-m1, EC-m2, EC-m3, EC-m4, EC-o, EC-ul, and EC-u2.

[0103] In embodiments, markers useful in the panels of the invention include markers for expression cluster Ec-i, namely, GRIK3, IQGAP2, FCER1G, STK32B, GADD45A, ITGAX, KLF3, RFTN1, PTK2, DFNB31, and ZMAT1, or a sub-set thereof, as well as the nucleic acid molecules encoding such proteins. In embodiments, levels of one or more of these markers are increased.

[0104] In embodiments, markers useful in the panels of the invention include markers for expression cluster EC-m1, namely, TFEC, COL18A1, SLC19A1, NRIP1, KCNH2, P2RX1, ARRDC5, BEX4, and APP, or a sub-set thereof, as well as the nucleic acid molecules encoding such proteins. In embodiments, levels of one or more of these markers are increased.

[0105] In embodiments, markers useful in the panels of the invention include markers for expression cluster EC-m2, namely, EML6, HCK, CD1C, VPS37B, CYBB, NXPH4, BTNL9, KLRK1, IQSECT, BANK1, LEF1, SH3D21, FMOD, SEMA4A, CTLA4, ADTRP, IGSF3, IGFBP4, PDGFD, and APOD, or a sub-set thereof, as well as the nucleic acid molecules encoding such proteins. In embodiments, levels of one or more of these markers are increased.

[0106] In embodiments, markers useful in the panels of the invention include markers for expression cluster EC-m3, namely, MS4A4E, MYL9, NT5E, MS4A6A, PITPNC1, CNTNAP2, 10 IGF2BP3, WNT3, CLDN7, TCF7, BASP1, FLJ20373, MAP4K4, LRRK2, SAMSN1, CEACAM1, TNFRSF13B, PHF16, MID1IP1, and ABCA9, or a sub-set thereof, as well as the nucleic acid molecules encoding such proteins. In embodiments, levels of one or more of these markers are increased.

[0107] In embodiments, markers useful in the panels of the invention include markers for expression cluster EC-m4, namely, MYBL1, NUGGC, GNG8, AEBP1, HIP1R, LATS2, RIMKLB, EML6, FADS3, MBOAT1, LCN10, DCLK2, and GLUL, or a sub-set thereof, as well as the nucleic acid molecules encoding such proteins. In embodiments, levels of one or more of these markers are increased.

[0108] In embodiments, markers useful in the panels of the invention include markers for expression cluster EC-o,

namely, ACSM3, TOX2, PHF16, SESN3, TBC1D9, PIP5K1B, SIK1, DUSP5, GNG7, HIVEP3, MARCKSL1, GPR183, HRK, and PITPNC1, or a sub-set thereof, as well as the nucleic acid molecules encoding such proteins. In embodiments, levels of one or more of these markers are increased.

[0109] In embodiments, markers useful in the panels of the invention include markers for expression cluster EC-ul, namely, SEPT10, LDOC1, LPL, KANK2, SOWAHC, DUSP26, OSBPL5, WNT9A, FGFR1, GTSF1L, ADD3, AKT3, COBLL1, MNDA, FCRL3, FAM49A, FCRL2, SLC2A3, and MARCKS, or a sub-set thereof, as well as the nucleic acid molecules encoding such proteins. In embodiments, levels of one or more of these markers are increased.

[0110] In embodiments, markers useful in the panels of the invention include markers for expression cluster EC-u2, namely, ITGB5, BCL7A, PPP1R9A, TSPAN13, SLC12A7, SSBP3, VASH1, SPG20, IL13RA1, NR3C2, TUBG2, ZNF804A, and IL2RA, or a sub-set thereof, as well as the nucleic acid molecules encoding such proteins. The panels can comprise biomarkers for expression cluster Ec-i, EC-m1, EC-m2, EC-m3, EC-m4, EC-o, EC-ul, or EC-u2, or various combinations thereof. In embodiments, levels of one or more of these markers are increased. By "fragment" is meant a portion of a polypeptide or nucleic acid molecule. This portion contains, preferably, at least 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, or 90% of the entire length of the reference nucleic acid molecule or polypeptide. A fragment may contain 10, 20, 30, 40, 50, 60, 70, 80, 90, or 100, 200, 300, 400, 500, 600, 700, 800, 900, or 1000 nucleotides or amino acids.

[0111] By "increase" is meant to alter positively An increase may be by about or at least about 0.5%, 1%, 5%, 10%, 25%, 30%, 50%, 75%, or even by 100%.

[0112] The terms "isolated," "purified," or "biologically pure" refer to material that is free to varying degrees from components which normally accompany it as found in its native state.

[0113] "Isolate" denotes a degree of separation from an original source or surroundings. "Purify" denotes a degree of separation that is higher than isolation. A "purified" or "biologically pure" protein is sufficiently free of other materials such that any impurities do not materially affect the biological properties of the protein or cause other adverse consequences. That is, a nucleic acid or peptide of this invention is purified if it is substantially free of cellular material, viral material, or culture medium when produced by recombinant DNA techniques, or chemical precursors or other chemicals when chemically synthesized. Purity and homogeneity are typically determined using analytical chemistry techniques, for example, polyacrylamide gel electrophoresis or high performance liquid chromatography. The term "purified" can denote that a nucleic acid or protein gives rise to essentially one band in an electrophoretic gel. For a protein that can be subjected to modifications, for example, phosphorylation or glycosylation, different modifications may give rise to different isolated proteins, which can be separately purified.

[0114] By "isolated polynucleotide" is meant a nucleic acid that is free of the genes which, in the naturally-occurring genome of the organism from which the nucleic acid molecule of the invention is derived, flank the gene. The term therefore includes, for example, a recombinant DNA that is incorporated into a vector; into an autonomously replicating plasmid or virus; or into the genomic DNA of a prokaryote or eukaryote; or that exists as a separate molecule (for example, a cDNA or a genomic or cDNA fragment produced by PCR or restriction endonuclease digestion) independent of other sequences. In addition, the term includes an RNA molecule that is transcribed from a DNA molecule, as well as a recombinant DNA that is part of a hybrid gene encoding additional polypeptide sequence.

[0115] By an "isolated polypeptide" is meant a polypeptide of the invention that has been separated from components that naturally accompany it. Typically, the polypeptide is isolated when it is at least 60%, by weight, free from the proteins and naturally-occurring organic molecules with which it is naturally associated. Preferably, the preparation is at least 75%, more preferably at least 90%, and most preferably at least 99%, by weight, a polypeptide of the invention. An isolated polypeptide of the invention may be obtained, for example, by extraction from a natural source, by expression of a recombinant nucleic acid encoding such a polypeptide; or by chemically synthesizing the protein. Purity can be measured by any appropriate method, for example, column chromatography, polyacrylamide gel electrophoresis, or by HPLC analysis.

[0116] By "marker profile" is meant a characterization of the expression or expression level of two or more polypeptides or polynucleotides in a sample.

[0117] As used herein, "obtaining" as in "obtaining an agent" includes synthesizing, purchasing, or otherwise acquiring the agent.

[0118] By "polypeptide" or "amino acid sequence" is meant any chain of amino acids, regardless of length or post-translational modification. In various embodiments, the post-translational modification is glycosylation or phosphorylation. In various embodiments, conservative amino acid substitutions may be made to a polypeptide to provide functionally equivalent variants, or homologs of the polypeptide. In some aspects, the invention embraces sequence alterations that result in conservative amino acid substitutions. In some embodiments, a "conservative amino acid substitution" refers to an amino acid substitution that does not alter the relative charge or size characteristics of the protein in which the conservative amino acid substitution is made.

[0119] Variants can be prepared according to methods for altering polypeptide sequence known to one of ordinary skill in the art such as are found in references that compile such methods, e.g.

[0120] Molecular Cloning: A Laboratory Manual, J. Sambrook, et al., eds., Second Edition, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989, or Current Protocols in Molecular Biology, F. M. Ausubel, et al., eds., John Wiley & Sons, Inc., New York. Non-limiting examples of conservative substitutions of amino acids include substitutions made among amino acids within the following groups: (a) M, I, L, V; (b) F, Y, W; (c) K, R, H; (d) A, G; (e) S, T; (f) Q, N; and (g) E, D. In various embodiments, conservative amino acid substitutions can be made to the amino acid sequence of the proteins and polypeptides disclosed herein.

[0121] "Primer set" means a set of oligonucleotides. A primer set may comprise at least about 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 30, 40, 50, 60, 80, 100, 200, 250, 300, 400, 500, 600, or more primers. In embodiments, the primers are used for detection of a biomarker(s) in a sample (e.g., by PCR,

targeted sequencing, biochip, or any of various other methods described herein or combinations thereof).

[0122] By "reduce" is meant to alter negatively. A reduction may be by about or at least about 0.5%, 1%, 5%, 10%, 25%, 30%, 50%, 75%, or even by 100%.

[0123] By "reference" is meant a standard or control condition. In embodiments, the reference is the level of an analyte present in a sample obtained from a subject prior to being administered a treatment, obtained from a healthy subject (e.g., a subject not having a chronic lymphocytic leukemia (CLL)), or a sample obtained from a subject at an earlier time point than a particular sample time point.

[0124] A "reference sequence" is a defined sequence used as a basis for sequence comparison. A reference sequence may be a subset of or the entirety of a specified sequence; for example, a segment of a full-length cDNA or gene sequence, or the complete cDNA or gene sequence. For polypeptides, the length of the reference polypeptide sequence will generally be at least about 16 amino acids, preferably at least about 20 amino acids, more preferably at least about 25 amino acids, and even more preferably about 35 amino acids, about 50 amino acids, or about 100 amino acids. For nucleic acids, the length of the reference nucleic acid sequence will generally be at least about 50 nucleotides, preferably at least about 60 nucleotides, more preferably at least about 75 nucleotides, and even more preferably about 100 nucleotides or about 300 nucleotides or any integer thereabout or therebetween.

[0125] By "specifically binds" is meant an agent that recognizes and binds a polypeptide or polynucleotide of the invention, but which does not substantially recognize and bind other molecules in a sample, for example, a biological sample, which naturally includes a polypeptide or polynucleotide described herein.

[0126] Nucleic acid molecules useful in the methods of the invention include any nucleic acid molecule that encodes a polypeptide of the invention or a fragment thereof. Such nucleic acid molecules need not be 100% identical with an endogenous nucleic acid sequence, but will typically exhibit substantial identity. Polynucleotides having "substantial identity" to an endogenous sequence are typically capable of hybridizing with at least one strand of a double-stranded nucleic acid molecule. By "hybridize" is meant to pair to form a double-stranded molecule between complementary polynucleotide sequences (e.g., a gene described herein), or portions thereof, under various conditions of stringency. (See, e.g., Wahl, G. M. and S. L. Berger (1987) Methods Enzymol. 152:399; Kimmel, A. R. (1987) Methods Enzymol. 152:507).

[0127] For example, stringent salt concentration will ordinarily be less than about 750 mM NaCl and 75 mM trisodium citrate, preferably less than about 500 mM NaCl and 50 mM trisodium citrate, and more preferably less than about 250 mM NaCl and 25 mM trisodium citrate. Low stringency hybridization can be obtained in the absence of organic solvent, e.g., formamide, while high stringency hybridization can be obtained in the presence of at least about 35% formamide, and more preferably at least about 50% formamide. Stringent temperature conditions will ordinarily include temperatures of at least about 30° C., more preferably of at least about 37° C., and most preferably of at least about 42° C. Varying additional parameters, such as hybridization time, the concentration of detergent, e.g., sodium dodecyl sulfate (SDS), and the inclusion or exclusion of carrier DNA, are well known to those skilled in the art. Various levels of stringency are accomplished by combining these various conditions as needed. In a preferred embodiment, hybridization will occur at 30° C. in 750 mM NaCl, 75 mM trisodium citrate, and 1% SDS. In a more preferred embodiment, hybridization will occur at 37° C. in 500 mM NaCl, 50 mM trisodium citrate, 1% SDS, 35% formamide, and 100 μg/ml denatured salmon sperm DNA (ssDNA). In a most preferred embodiment, hybridization will occur at 42° C. in 250 mM NaCl, 25 mM trisodium citrate, 1% SDS, 50% formamide, and 200 μg/ml ssDNA. Useful variations on these conditions will be readily apparent to those skilled in the art.

[0128] For most applications, washing steps that follow hybridization will also vary in stringency. Wash stringency conditions can be defined by salt concentration and by temperature.

[0129] As above, wash stringency can be increased by decreasing salt concentration or by increasing temperature. For example, stringent salt concentration for the wash steps will preferably be less than about 30 mM NaCl and 3 mM trisodium citrate, and most preferably less than about 15 mM NaCl and 1.5 mM trisodium citrate. Stringent temperature conditions for the wash steps will ordinarily include a temperature of at least about 25° C., more preferably of at least about 42° C., and even more preferably of at least about 68° C. In a preferred embodiment, wash steps will occur at 25° C. in 30 mM NaCl, 3 mM trisodium citrate, and 0.1% SDS. In a more preferred embodiment, wash steps will occur at 42° C. in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. In a more preferred embodiment, wash steps will occur at 68° C. in 15 mM NaCl, 1.5 mM trisodium citrate, and 0.1% SDS. Additional variations on these conditions will be readily apparent to those skilled in the art. Hybridization techniques are well known to those skilled in the art and are described, for example, in Benton and Davis (Science 196:180, 1977); Grunstein and Hogness (Proc. Natl. Acad. Sci., USA 72:3961, 1975); Ausubel et al. (Current Protocols in Molecular Biology, Wiley Interscience, New York, 2001); Berger and Kimmel (Guide to Molecular Cloning Techniques, 1987, Academic Press, New York); and Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratory Press, New York.

[0130] By "substantially identical" is meant a polypeptide or nucleic acid molecule exhibiting at least 50% identity to a reference amino acid sequence (for example, any one of the amino acid sequences described herein) or nucleic acid sequence (for example, any one of the nucleic acid sequences described herein). In embodiments, such a sequence is at least 60%, 80%, 85%, 90%, 95% or even 99% identical at the amino acid level or nucleic acid to the sequence used for comparison.

[0131] Sequence identity is typically measured using sequence analysis software (for example, Sequence Analysis Software Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, Wis. 53705, BLAST, BESTFIT, GAP, or PILEUP/PRETTYBOX programs). Such software matches identical or similar sequences by assigning degrees of homology to various substitutions, deletions, and/or other modifications. Conservative substitutions typically include substitutions within the following groups: glycine, alanine; valine, isoleucine, leucine; aspartic acid, glutamic acid, asparagine, glutamine; serine, threonine; lysine, arginine;

and phenylalanine, tyrosine. In an exemplary approach to determining the degree of identity, a BLAST program may be used, with a probability score between e^{-3} and e^{-100} indicating a closely related sequence.

[0132] By "subject" is meant an animal. The animal can be a mammal. The mammal can be a human or non-human mammal, such as a bovine, equine, canine, ovine, rodent, or feline.

[0133] Ranges provided herein are understood to be shorthand for all of the values within the range. For example, a range of 1 to 50 is understood to include any number, combination of numbers, or sub-range from the group consisting of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, or 50.

[0134] As used herein, the terms "treat," treating," "treatment," and the like refer to reducing or ameliorating a disorder and/or symptoms associated therewith. It will be appreciated that, although not precluded, treating a disorder or condition does not require that the disorder, condition or symptoms associated therewith be completely eliminated.

[0135] Unless specifically stated or obvious from context, as used herein, the term "or" is understood to be inclusive. Unless specifically stated or obvious from context, as used herein, the terms "a", "an", and "the" are understood to be singular or plural.

[0136] Unless specifically stated or obvious from context, as used herein, the term "about" is understood as within a range of normal tolerance in the art.

[0137] The recitation of a listing of chemical groups in any definition of a variable herein includes definitions of that variable as any single group or combination of listed groups. The recitation of an embodiment for a variable or aspect herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

[0138] Any compositions or methods provided herein can be combined with one or more of any of the other compositions and methods provided herein.

BRIEF DESCRIPTION OF THE DRAWINGS

[0139] FIG. **1** provides a schematic overview of a design for a functional precision study integrating high-throughput dynamic BH3 profiling (HT-DBP) (top portion of FIG. **1**) and molecular profiling (lower portion of FIG. **1**). BH3 profiling is a functional tool that measures mitochondrial apoptotic priming. It uses BH3 peptides derived from the BH3 domain of pro-apoptotic BH3-only proteins to provoke a response from viable mitochondria.

[0140] FIGS. **2**A and **2**B provide a genomic landscape diagram and a bar graph. FIG. **2**A provides a genomic landscape diagram providing an overview of a chronic lymphocytic leukemia (CLL) cohort (68 samples; 65 patients (+3 pre/post treatment); 64 in CLL-map). For FIG. **2**A, whole-exome sequencing/whole genome sequencing (WES/WGS) (n=61), RNA (n=57, 10 new), methylation (n=47), CW22 (U-CLL) treatment was FCR, CW32 (U-CLL) treatment was FR_REV (later F_REV, FCR, BR+PCI), and CW48 (M-CLL) treatment was R (later R, FR). The cohort represented in FIGS. **2**A and **2**B was enriched in M-CLLs and all epitypes and expression clusters (ECs) were represented. FIG. **2**B provides a bar graph providing a breakdown of the numbers of different expression clusters observed within the CLL cohort.

[0141] FIG. **3** provides a schematic providing an overview of the high-throughput dynamic BH3 profiling (HT-DBP) screen.

[0142] FIG. **4** provides a schematic illustration of the anti-apoptotic proteins targeted by the different BH3 peptides used in the HT-DBP screen. Peptides that were promiscuous in the anti-apoptotic proteins that they targeted were considered "activators" and peptides that were selective in the anti-apoptotic proteins that they targeted were considered "sensitizers." Different peptides, therefore, provided different information with regard to a drug's impact on a CLL cell.

[0143] FIGS. **5**A and **5**B provide plots demonstrating that dynamic BH3 profiling screens gave high quality and reproducible results. In FIG. **5**A, each point is the mean of 3 replicate comparisons per plate (A-vs-B, A-vs-C, B-vs-C). Replicates correlated across patients.

[0144] FIGS. **6**A and **6**B provide a heat map and a dendrogram. FIG. **6**A provides a heatmap that shows BH3 peptide effect similarity based on Pearson's correlations across different drugs across patients. PUMA, BIM—non-specific; BAD-BCL2 inhibitor; MS1-MCL1 inhibitor. FIG. **6**B provides a dendrogram showing peptide effect similarity.

[0145] FIGS. **7**A, **7**B, and **7**C provide a schematic and heatmaps showing the landscape of response in CLL samples. FIG. **7**A provides a schematic comparing the positive delta-priming (i.e., priming of an apoptosis in the presence of an agent for treating CLL as compared to priming in the presence of DMSO) values observed for cells contacted with the indicated BH3 peptides at the indicated concentrations in combination with the 42 drugs evaluated. FIGS. **7**B and **7**C provide heat maps showing that delta priming values were consistent for each indicated drug (left of heat maps) across all of the evaluated BH3 peptides (top of heat maps). Current first-line treatments for CLL include Venetoclax and/or Ibrutinib, which fell within the top-ten drugs with the highest positive delta priming values.

[0146] FIGS. **8**A and **8**B provide histograms showing that dynamic BH3 profiling screens provided combination therapy leads. FIG. **8**A provides a histogram showing that a combined treatment involving administration of Venetoclax (BCL2 inhibitor) and MS1 (MCL1 inhibitor) had an increased delta priming value relative to alternative treatments. FIG. **8**B provides a histogram showing that a combined treatment involving Iburtinib (Bruton's tyrosine kinase (BTK) inhibitor) and BAD (BCL2 inhibitor) had an increased delta priming value relative to alternative treatments. DBP can be used to evaluate efficacy of such combination therapies in a clinical setting (e.g., Venetoclax combined with an MCL1 inhibitor, such as AZD5991, or Iburtinib combined with a BCL2 inhibitor, such as Venetoclax).

[0147] FIG. **9** provides a plot showing drugs that had high median delta priming in the U-CLL IGHV subtype (drugs with points above diagonal line) and drugs that had high median delta priming in the M-CLL IGHV subtype (drugs with points below diagonal line).

[0148] FIGS. **10**A, **10**B, 1° C. and 1OD provide a consensus matrix, a heat map, stacked bar plots, a scatter plot, and a line plot showing that gene expression clusters (ECs) revealed 8 distinct chronic lymphocytic leukemia (CLL) subtypes. 2 IGHV-unmutated/n-CLL clusters; 4 IGHV-mu-

tated/m-CLL clusters; EC-i associated with i-CLL and IGLV3-21 R110 mutations; EC-m2 & EC-u2: tri(12)-enriched. FIG. **10**A provides a consensus matrix for RNA expression profiles of 610 treatment-naive CLLs by repeated hierarchical clustering with 80% resampling and varying cutoffs for number of clusters. This matrix served as input to a Bayesian non-negative matrix factorization (BayesNMF) method for inferring the total number of clusters and sample assignment to clusters. FIG. **10**B provides a heat map and a stacked bar graph together showing eight gene expression clusters (ECs, columns) identified by a Bayesian non-negative matrix factorization (BNMF) method in 610 treatment-naive samples. FIG. **10**C provides a plot showing a Kaplan Meier analysis of the impact of expression clusters on overall survival (OS) probabilities in 609 treatment-naive samples (log-rank test). FIG. **10**D provides a plot showing uniform manifold approximation and projection (UMAP) showing clustering of expression clusters (ECs).

[0149] FIG. **11** provides a dendrogram that shows, together with FIG. **10**B, that the expression clusters were distinguished by molecular features and drivers. FIG. **11** provides a dendrogram of expression clusters (ECs) with associated upregulated and downregulated biologic pathways determined by gene set enrichment analysis. The clusters varied in size and are segregated by biological features and defined subtypes of the IGHV subtypes: 2 clusters, represent U-CLLs, which give them the EC-u prefix. 4 clusters given the EC-m prefix, were strongly associated with mutated IGHV. The last cluster, named EC-i, was associated with the intermediate methylation subtype. The clusters differed by their genetic driver landscapes: a) EC-m2 and EC-u2 were strongly associated with tri(12) events, jointly containing>85% of tri(12) events; b) EC-i was defined by a specific variant in the Ig light chain, which led to constitutive B-cell receptor signaling and was shown to be associated with adverse outcome. There were 4 EC-ms, 2 EC-us, and 2 ECs that associated with tri(12). Some ECs were more defined by unique pathways, such as enhanced Oxphos in what was named EC-o and Inflammatory signaling in EC-m4. Some pathways helped distinguish between clusters of the same IGHV subtype. For example, both U-CLL clusters shared downregulation of translation, but differed in TNF-alpha signaling. Also, among M-CLLs, EC-m2 had increased antigen processing and presentation via HLA class 1b, whereas in EC-m3 this was lower. These nonclassical HLAs are thought to play a role in immune escape and are associated with poor prognosis.

[0150] FIGS. **12**A, **12**B and **12**C provide plots showing dynamic BH3 profiling responses per CLL expression subtype.

[0151] FIG. **13** provides a schematic showing how drug sensitivity experiment data can be used to inform differential effects among expression clusters. Experimental data available includes that from 246 blood cancers, 184 CLLs, and 136 CLLs with RNA-seq. See, Dietrich, et al. "Drug-perturbation-based stratification of blood cancer," JCI, 128: 427-445 (2018), the disclosure of which is incorporated herein by reference in its entirety for all purposes.

[0152] FIG. **14** provides a heatmap showing median delta-priming for the indicated molecular features. Molecular features shown in FIG. **14** include IGHV subtypes, epitypes, expression subtypes (i.e., expression clusters), mutations in driver genes, and recurrent copy-number events. A feature was included in the heatmap of FIG. **14** only if at least 2 patients in a DBP screen had the feature. Median delta-priming was computed across all BH3 peptides and across all patients within the feature.

[0153] FIG. **15** provides a plot comparing DBP z-scores for U-CLL and viability z-scores for U-CLL.

[0154] FIG. **16** provides a plot comparing DBP z-scores for M-CLL and viability z-scores for M-CLL.

[0155] FIG. **17** provides a heatmap showing median delta priming across healthy donors for the indicated normal cell types (CD14, CD19, and CD3).

[0156] FIG. **18** provides a heatmap showing values calculated by subtracting the median delta priming values for normal cell types ("Normals") from median delta-priming for the indicated molecular features. The "Normals" column in FIG. **18** is the median delta-priming value across all peptides, donors and sample types (CD19, CD3, CD14). All other columns contain median delta-priming values for tumors associated with the denoted molecular feature after subtracting the value in the Normals column.

[0157] FIG. **19** provides a comut plot showing molecular features for a group of n=65 patients.

[0158] FIG. **20** provides a comut plot showing molecular features for a group of n=81 patients.

[0159] FIGS. **21**A and **21**B provide a heatmap and dendrogram showing peptide effect similarity for multiple peptide concentrations. PUMA 1 μM, BIM 0.01 μM, BAD 0.3 μM and MSI 2.5 μM groups were used in several analyses as part of the examples disclosed herein.

[0160] FIGS. **22**A and **22**B provide a heatmap and plot comparing median delta priming for several drugs of interest.

[0161] FIG. **23** provides a plot showing differential drug sensitivity of several expression clusters of interest. Here, a published dataset of 136 CLL patients with RNA-seq whose samples were screened with 63 drugs was used. The expression cluster classifier was applied to the RNA-seqs and the data was used to show differential sensitivity of the ECs to these different drugs, such that patients with relevant mutations could be efficaciously treated by a drug for which sensitivity is high (for example, Venetoclax).

[0162] FIGS. **24**A, **24**B, **24**C and **24**D provide plots comparing drug sensitivity results in M-CLL and U-CLL groups by comparing, at the same concentration, the mean of the two closest (higher and lower) z-scored medians or z-scored means.

[0163] FIG. **25** provides a table identifying Venetoclax sensitivities for different driver alterations at different peptide concentrations. The table identifies if the priming response exhibited by each combination indicates that a patient with the associated driver alterations would likely respond favorably to treatment, or if they would be resistant to the drug being used.

[0164] FIG. **26** provides a table identifying kinase inhibitor drug sensitivities for different peptide concentrations and driver alterations.

[0165] FIG. **27** provides a table showing the relative efficacy of Abxinostat under conditions where patients are likely to be resistant to drugs such as Nutlin-3, MK-2206, and Zanubrutinib.

[0166] FIG. **28** provides a table showing that certain BCL2 inhibitors, such as Venetoclax, can exhibit similar priming responses when combined with peptides have a BCL2 inhibiting effect, which can assist in the identification of new CLL therapies.

[0167] FIG. **29** provides a schematic illustration of the anti-apoptotic proteins targeted by the different BH3 peptides used in DBP screening; because the different peptides could be relatively more or less selective for the anti-apoptotic proteins they targeted, use of each of the peptides provided different information with regard to a drug's impact on a CLL cell.

[0168] FIG. **30** provides a table showing that MCL1 inhibitors, approximated here with the presence of MS1 peptide, likely exhibit strong effects as part of combination therapies when used together.

[0169] FIG. **31** provides a clustered heatmap showing the level of association (Pearson correlation) of each molecular feature (IGHV, or epitype, or EC subtypes and drivers) with delta-priming across the CLL samples with 0.3 μM BAD when using delta priming as a categorical variable (high>10, vs. low<5).

[0170] FIG. **32** provides a clustered heatmap showing the level of association (Pearson correlation) of each molecular feature (IGHV, or epitype, or EC subtypes and drivers) with delta-priming across the CLL samples with 0.01p M BIM when using delta priming as a categorical variable (high>10, vs. low<5).

[0171] FIG. **33** provides a clustered heatmap showing the level of association (Pearson correlation) of each molecular feature (IGHV, or epitype, or EC subtypes and drivers) with delta-priming across the CLL samples with 2.53 μM MS1 when using delta priming as a categorical variable (high>10, vs. low<5).

[0172] FIG. **34** provides a clustered heatmap showing the level of association (Pearson correlation) of each molecular feature (IGHV, or epitype, or EC subtypes and drivers) with delta-priming across the CLL samples with 1 μM PUMA when using delta priming as a categorical variable (high>10, vs. low<5).

[0173] FIG. **35** provides a clustered heatmap showing the level of association (Pearson correlation) of each molecular feature (IGHV, or epitype, or EC subtypes and drivers) with delta-priming across the CLL samples with 0.3 μM BAD as a continuous variable (using all values).

[0174] FIG. **36** provides a clustered heatmap showing the level of association (Pearson correlation) of each molecular feature (IGHV, or epitype, or EC subtypes and drivers) with delta-priming across the CLL samples with 0.01 μM BIM as a continuous variable (using all values).

[0175] FIG. **37** provides a clustered heatmap showing the level of association (Pearson correlation) of each molecular feature (IGHV, or epitype, or EC subtypes and drivers) with delta-priming across the CLL samples with 2.5p M MS1 as a continuous variable (using all values).

[0176] FIG. **38** provides a clustered heatmap showing the level of association (Pearson correlation) of each molecular feature (IGHV, or epitype, or EC subtypes and drivers) with delta-priming across the CLL samples with 1 μM PUMA as a continuous variable (using all values).

[0177] FIG. **39** provides a heatmap showing median delta-priming for the indicated molecular features.

[0178] FIG. **40** provides a heatmap showing median delta-priming across healthy donors per normal cell type.

[0179] FIG. **41** provides a heatmap showing median delta-priming for the indicated molecular features.

DETAILED DESCRIPTION OF THE INVENTION

[0180] The invention features, among other things, compositions, panels of biomarkers, and methods for selecting a subject with chronic lymphocytic leukemia (CLL) for treatment using an agent and/or for inclusion in a clinical trial using the agent to treat CLL. Also provided herein are methods and compositions for treatment prioritization, treatment sequencing, pharmacotyping, and/or drug repurposing for CLL.

[0181] The invention is based, at least in part, on the findings presented in the Examples provided herein based on a dynamic BH3 profiling (DBP) drug screen used to assess the relative sensitivity of many CLL patient samples to an array of drugs. These sensitivities of CLL samples were compared to normal B-cell samples to evaluate the extent to which the effect of each drug was specific to diseased cells. Of note, B-cells are non-essential to the survival of the subject and, therefore, drugs that effectively lead to apoptosis of both normal and leukemic B-cells should not be ruled out as potentially valid treatment options. Applying DBP to a large set of CLL samples, assisted by High-throughput DBP (HT-DBP) enabled pharmacotyping (i.e., identifying groups of samples that were responsive or unresponsive to one or more drug treatments). Pharmacotyping can be utilized for prognosis and diagnosis, in addition to treatment assignment.

[0182] In embodiments, CLL is characterized using eight chronic lymphocytic leukemia (CLL) gene expression subtypes and their efficacy in guiding prognosis and selection of subjects for a treatment. Not being bound by theory, the gene expression subtypes correspond to gene expression clusters enriched with unique genetic and epigenetic features, distinguished by cellular pathways, and useful as an independent prognostic factor. A machine classifier was developed to classify a chronic lymphocytic leukemia (CLL) as belonging to a particular gene expression subtype associated with a corresponding gene expression cluster. The gene expression clusters and their corresponding expression subtypes are termed Ec-i, EC-m1, EC-m2, EC-m3, EC-m4, EC-o, EC-ul, and EC-u2. Said expression subtypes are known in the art and described, for example, by Knisbacher et al., Nat Genet. 2022 November; 54(11): 1664-1674., and in PCT/US2021/045144 (BI-10756), filed Aug. 9, 2021, each of which is incorporated herein by reference in its entirety. In embodiments, the gene expression subtype is used in combination with genetic drivers and epigenetic states in a model to assist in predicting sensitivity of a CLL to a drug. In embodiments, subjects with a CLL predicted to be sensitive to a particular drug are administered the drug as part of a treatment for the CLL.

[0183] Dynamic BH3 Profiling Dynamic BH3 profiling (DBP) is a drug screening assay that measures the relative priming of cells in a biological sample for cell death by apoptosis in the presence of a specific compound and/or a pro-apoptotic peptide. By "Dynamic BH3 profiling" is meant measuring drug-induced changes in mitochondrial apoptotic priming. Mitochondrial apoptotic priming is a measure of how close to the apoptotic threshold a cell is. A highly primed cell has relatively less anti-apoptotic binding site availability and is closer to the apoptotic threshold than a poorly primed cell, which has more anti-apoptotic availability to buffer an apoptotic assault and is further from the apoptotic threshold. BH3 peptides derived from the BH3

domain of pro-apoptotic BH3-only proteins provoke a response from viable mitochondria. Cytochrome c released from the mitochondria after a short incubation with BH3 peptide is used as a surrogate for priming. In general, the more sensitive a mitochondrion is to a BH3 peptide, the more primed it is. A drug treatment that enhances priming will cause mitochondria to undergo MOMP more easily when incubated with a fixed concentration of a promiscuously binding BH3 peptide, such as BIM BH3 peptide, compared to control-treated cells. See, for example, Potter, D. S. & Letai, A. To prime, or not to prime: that is the question. Cold Spring Harb. Symp. Quant. Biol. 81, 131-140 (2016); Montero, J. et al. Drug-induced death signaling strategy rapidly predicts cancer response to chemotherapy. Cell 160, 977-989 (2015); Daniels, V. W. et al. Metabolic perturbations sensitize triple-negative breast cancers to apoptosis induced by BH3 mimetics. Sci.

[0184] Signal 14, eabc7405 (2021); Bhola, P. D. et al. High-throughput dynamic BH3 profiling may quickly and accurately predict effective therapies in solid tumors. Sci. Signal 13, eaayl451 (2020); and Potter, D. S., Du, R., Bhola, P., Bueno, R. & Letai, A. Dynamic BH3 profiling identifies active BH3 mimetic combinations in non-small cell lung cancer. Cell Death Dis. 12, 741 (2021).

[0185] Dynamic BH3 profiling and peptides for use therein are described, for example, in Certo, et al., "Mitochondria primed by death signals determine cellular addiction to antiapoptotic BCL-2 family members," Cancer Cell, 9:351-365 (2006); and in Foight, et al. "Designed BH3 Peptides with High Affinity and Specificity for Targeting Mcl-1 in Cells," ACS Chemical Biology, 9:1962-1968 (2014), the disclosures of which are incorporated herein by reference in their entireties for all purposes. The DBP assay enables one to compare the response of a patient tumor sample to a specific drug relative to other drugs and relative to an inert control (e.g., DMSO). Similarly, DBP allows one to evaluate sensitivity of a leukemia sample to various pro-apoptotic peptides, which can be promiscuous activators of apoptosis (BIM and PUMA which both target e.g., BCL-2, BCL-XL and MCL-1) or selective activators of apoptosis (BAD which targets BCL-2 and BCL-XL; and MS1 which targets MCL-1). Drug and peptide combinations that are effective only or especially when administered at the same time can be detected as well.

Chronic Lymphocytic Leukemia (CLL)

[0186] Chronic lymphocytic leukemia (CLL) is a type of cancer in which the bone marrow makes too many lymphocytes. Early on there are typically no symptoms. Later, non-painful lymph node swelling, feeling tired, fever, night sweats, or weight loss for no clear reason may occur. Enlargement of the spleen and low red blood cells (anemia) may also occur. It typically worsens gradually (i.e., "chronic") over years.

[0187] Chronic lymphocytic leukemia (CLL) is a B cell neoplasm with variable natural history that is conventionally categorized into two major subtypes distinguished by the extent of somatic mutations in the heavy chain variable region of immunoglobulin genes (IGHV).

Selection of Subjects for Treatment

[0188] Panels comprising biomarkers of the invention are used to characterize chronic lymphocytic leukemia (CLL) in a subject to select the subject for treatment with an agent, for prognosis, and/or to characterize the CLL as belonging to an expression subtype (e.g., Ec-i, EC-m1, EC-m2, EC-m3, EC-m4, EC-o, EC-ul, and/or EC-u2). The panels of the invention are used in combination with a classification model, as described in the Examples provided herein, to categorize a chronic lymphocytic leukemia as belonging to an expression subtype selected from Ec-i, EC-m1, EC-m2, EC-m3, EC-m4, EC-o, EC-ul, and EC-u2. In certain embodiments, panels of the invention are used to select a treatment for the subject. In some embodiments, panels of the invention are used to select a subject for inclusion in a clinical study; for example, a subject is selected for treatment if the subject has a CLL of an expression subtype associated with a positive response to a drug being evaluated in the clinical study. In embodiments, the expression subtype is used as an input to an integrated model for predicting a clinical outcome for a subject having CLL. The integrated model can include as inputs, expression subtype, genetic drivers, and epigenetic states.

[0189] Non-limiting examples of genetic drivers include DNA mutations, copy number alterations, and/or structural variants in one or more of the following genes and/or genomic 10 regions: Genes: ADAMTS4, ANK], ARIDIA, ARID5B, ARPC4, ASXL1, ATM, BAI2, BAZ2A, BCOR, BIRC3, BRAF, BRCC3, CARD]], CCND2, CDC25B, CDCA7, CDKN]B, CENPB, CHD2, CHKB, CNOT3, CREB1, CREBBP, CUL9, DDX3X, DICER1, DIS3, DYRKIA, EEFIA1, EGR2, EWSR1, FAM50A, FAM65C, FBXW7, FUBPJ, GNBI, GPS2, GSR, IKBKB, IKZF3, INO80, IRF4, ITIH2, ITPKB, KLHL6, KMT2D, KRAS, MAP2K1, MAP2K2, MAP4K5, MAPK4, MBDI, MED], MED12, MGA, MSL3, MUM], MYD88, MYLK4, NCAPG, NEK8, NFKBI, NFKBIB, NFKBIE, NOTCH], NRAS, NSD], NXF], POLR3B, POT], PTPN]], RAF], RELA, RFX7, RPS]5, RPS16, RPS23, RRMI, RSC]A], RUFY], SAMHDI, SCN8A, SENP7, SETD2, SF3B1, SP140, SPEN, TFCP2, TP53, TRAF3, TRMT1, USP8, XPOI, ZC3H18, ZMYM3, and ZNF292; Genomic regions: I0p12.2, 10q21.3, 10q24.2, 10q24.32, 11q, 1113.4, 11q22.3, 12pl3.31, 12pl3.31, 13q14.13, 13q14.2, 13q14.3, 14q32.12, 14q32.33, 15q15.1, 15q24.2, 15q25.2, 15q26.1, 16p11.2, 16p11.2, 16pl3.3, 16q22.1, 17p, 17p11.2, 17p13.1, 17p13.3, 17q, 17q11.2, 17q21.32, 17q22, 17q23.1, 17q23.3, 17q25.1, 18p, 18q11.2, 18q21.2, 19p, 19p13.11, 19pl3.12, 19pl3.3, 19q, 19q13.33, lp31.3, lp35.2, 1p36.11, p360.21, 1921.3, 1q22, 1923.2, 1932.2, 1942.12, 1942.13, 20p, 20p11.22, 22q12.1, 22q13.2, 2p, 2p11.2, 2p13.3, 2p15, 2p23.3, 2q12.2, 2q13, 2q31.1, 3p, 3p13, 3p21.31, 3p22.2, 3p22.3, 4p, 4q35.1, 5pl5.33, 5q32, 5q35.3, 6p21.32, 6p22.1, 6q, 6q21, 6q25.3, 7p22.1, 7p22.2, 7q11.23, 7q22.1, 7q36.1, 8p, 8p11.23, 8q, 8q12.1, 8q22.1, 9p21.3, and 9q34.3, 12 (including trisomy of chromosome 12).

[0190] In some embodiments, results from a dynamic BH3 profiling (DBP) and/or high-throughput DBP (HT-DBP) screen, as described in the Examples provided herein, can be compared to existing or future DBP and/or HT-DBP screens to assign a subject's CLL to a specific pharmacotype and to prioritize treatment.

[0191] In some embodiments, a specific treatment plan is advised or disadvised for subjects with a specific subtype of CLL. Subtypes include but are not limited to IGHV-mutated CLL (M-CLL), IGHV-unmutated CLL (U-CLL), methylation subtypes of CLL [CLLs that resemble naive B-cells

(n-CLL), intermediate methylation state CLLs (i-CLL) and/or CLLs that resemble memory B-cells (m-CLL)], RNA expression subtypes (EC-m1, EC-m2, EC-m3, EC-m4, EC-ul, EC-u2, EC-o, EC-i, and/or the more general EC-m and/or EC-u).

[0192] In some embodiments, treatments are recommended for subjects whose CLL has a specific genetic mutation, genetic copy-number alteration and/or a genetic structural variation that is associated with a response or lack of response to one or more specific drugs or drug classes. These alterations can arise in the germline or somatically in the leukemic cells or the leukemia's precursor cells.

[0193] In some embodiments, the method comprises determining whether a subject sample (e.g., a CLL sample) will or will not respond to a specific drug or drug class. In certain embodiments, the drugs comprise Abexinostat, Acalabrutinib, Azacitidine, AZD8055, Carfilzomib, Cerdulatinib, Crizotinib, Dasatinib, Duvelisib, Entospletinib, Erastin, Fludarabine, Gandotinib, GSK690693, Idelalisib, JQ1, Lenalidomide, MK2206, Navitoclax, Nirogacestat, Nutlin-3, Osimertinib, Ponatinib, Rapamycin, Ricolinostat, Ruxolitinib, Selinexor, Sorafenib, Sunitinib, Umbralisib, Vecabrutinib, Vorinostat, A-1331852, atorvastatin, AZD5991, Bendamustine, Onalespib, Trametinib, Voruciclib, Zanubrutinib, Ibrutinib, and/or Venetoclax.

[0194] In some embodiments, response or resistance to these drugs extends to drug classes they represent and/or to other drugs that target the same molecules, processes and/or biological pathways, including for example those listed in Table 1A or Table 1B.

[0195] In some embodiments, the methods further comprise obtaining the sample (e.g., the cancer sample) from a subject. In certain embodiments, the method further comprises treating CLL and/or CLL subtypes U-CLL, M-CLL, n-CLL, i-CLL, m-CLL, EC-m1, EC-m2, EC-m3, EC-m4, EC-ul, EC-u2, EC-o, EC-i) in the subject by administering cancer therapy to the subject (e.g., a chemotherapy, a radiation therapy, an immunotherapy).

[0196] In some embodiments the method comprises administering a combination of drugs concurrently or defining a set of drugs to administer sequentially. In embodiments, the combination of drugs comprises two or more drugs listed in Table 1A or 1B. In some instances, the method comprises administering venetoclax to a subject in combination with an MCL1 inhibitor (e.g., AZD5991). In some cases, the method comprises administering iburtinib to a subject in combination with a BCL2 inhibitor (e.g., venetoclax). In embodiments, the BCL2 inhibitor comprises venetoclax, ZN-d5 (Zentalis), lisaftoclax (APG-2575, Ascentage), S55746 (Servier/Novartis), and/or AZD4320 (Astra-Zeneca). In some cases, the MCL1 inhibitor comprises AZD5991, tapotoclax (AMG-176, AMGEN), MIK665 (Servier/Novartis), A-1210477 (AbbVie), ANJ810 (Anji Oncology), PRT1419 (Prelude Therapeutics), AS00491, APG-3526 (Ascentage Pharma), CT-03, and//or CPT-6281 (Captor Therapeutics).

[0197] In some embodiments, DBP and/or HT-DBP is applied to determine the pharmacotype of a subject, which can be used for designing a treatment plan, prognosis and/or diagnosis as CLL or a molecular subtype of CLL.

[0198] In some embodiments, DNA sequencing, RNA sequencing, DNA methylation assays (e.g., reduced-representation bisulfite sequencing, methylation arrays, whole-genome bisulfite sequencing, targeted bisulfite sequencing) and/or proteomics are applied to a sample from a subject to recommend or unrecommend treatment with one or more of the aforementioned drugs.

[0199] The invention provides methods for using the expression subtype of a chronic lymphocytic leukemia (CLL) to predict the sensitivity or resistance of a CLL to a drug. The invention further provides methods for selecting a subject with chronic lymphocytic leukemia (CLL) for treatment with a drug to which the CLL is predicted to be sensitive. The invention also provides methods for selecting subjects having chronic lymphocytic leukemia for inclusion in a clinical trial or other drug study where subjects with CLL predicted to be sensitive to a drug being studied in the trial or study are included in the trial or study and/or subjects with CLL predicted to be resistant to the drug are excluded from the trial or study.

[0200] Based on their expression subtype, subjects are selected for treatment with one or more of the agents listed in Table 1A or 1B.

[0201] In some embodiments, a subject having a CLL with a particular expression subtype is selected for treatment with an agent targeting a gene or polypeptide associated with the expression subtype. In various embodiments, the association of a gene or polypeptide with an expression subtype is determined according to the associations (e.g., increase or decrease in expression levels) indicated in Table 3A.

[0202] In some embodiments, a subject having a CLL determined to have a driver mutation, is administered an agent targeting the gene and/or a product of the gene (e.g., an agent reducing expression or activity of the gene and/or polypeptide). In embodiments, the drug sensitivity and drug resistance information provided in FIGS. **12**A-**12**C relating to particular drugs and expression subtypes can be extrapolated to apply to those drugs having a similar or the same main target, and/or the same target category (A) or (B) as a drug listed in.

[0203] The correlation of test results with an expression subtype involves applying a classification algorithm (e.g., a machine learning classifier) of some kind to the results to determine the expression subtype. The classification algorithm may be as simple as determining whether or not the amounts of the markers are above or below a particular cut-off number. When multiple biomarkers are used, the classification algorithm may be a linear regression formula.

[0204] Alternatively, the classification algorithm may be the product of any of a number of learning algorithms described herein.

[0205] In the case of complex classification algorithms, it may be necessary to perform the algorithm on the data, thereby determining the expression subtype using a computer, e.g., a programmable digital computer. In either case, one can then record the status on tangible medium, for example, in computer-readable format such as a memory drive or disk or simply printed on paper. The result also could be reported on a computer screen.

[0206] Panels The present disclosure provides panels of biomarkers and the use of such panels for characterizing chronic lymphocytic leukemia (CLL). As would be understood, references herein to a biomarker, a panel of biomarkers, or other similar phrase indicates one or more of the biomarkers listed below, in Tables 3A and 4, or otherwise described herein.

[0207] In one embodiment, markers useful in the panels of the invention include, for example, ABCA9, ACAP3,

ACSM3, ADAP2, AF127936.7, ARHGAP33, ARMC7, ARRDC5, ARSD, ARSI, ASB2, ATP1A3, ATP2B1, ATPIF1, BASP1, BCL2A1, BCL7A, BCS1L, CAMK2A, CLDN23, CMTM7, COBLL1, CRELD2, CRY1, CTAGE9, CTLA4, DDR1, DKFZP761J1410, DPF3, EML6, ERRFIl, ESPNL, EZH2, FAHD2B, FAM109A, FBXO27, FGL2, FLJ20373, FMOD, GADD45A, GNAO1, GPR160, GPR34, GUCD1, HCK, HDAC4, HIP1R, HMCES, IGSF3, IQSEC1, ITGAX, KCNH3, KCNN3, KCTD3, KDM1B, KLK1, KSR1, LCN10, LINC00865, LPL, LRRK2, LUZP1, MAP4K4, MAPK4, MAST4, MPRIP, MRO, MSI2, MVB12B, MYBL1, MYC, MYL5, MYL9, MYO3A, NEDD9, NFKBIZ, NR2F6, NRIP1, NRSN2, NUGGC, P2RX1, *PELI*3, PIGB, PIP5K1B, PITPNC1, PLD1, PTPN7, QDPR, REPS2, RHBDF2, RIMKLB, RP11-134N1.2, RP11-265P11.1, RP11-453F18__B.1, RP11-456H18.2, RP1-90J20.12, SAMSN1, SCPEP1, SH3D21, SLC44A1, SLC4A7, SLC4A8, SMIM10, SPN, SSBP3, STAM, STX5, SYNGR3, TAS1R3, TBC1D2B, TBC1D9, TFEC, TIMELESS, TNFRSF13B, TNR, TOX2, TRIM7, TUBG2, VSIG10, WNT5A, ZMYND8, and ZNF804A, or a sub-set thereof, as well as the nucleic acid molecules encoding such proteins. In another embodiment, markers useful in the panels of the invention include, for example, ACAP3, ACSM3, AEBP1, AKT3, ARHGAP33, ARHGAP42, ARMC7, ARRDC5, ATPIF1, BACH2, BASP1, BCL7A, C17orfl00, CBLB, CD72, CD86, CEACAMI, CHPT1, CLDN7, CMTM7, CNTNAP1, COBLL1, COL18A1, CRY1, CTLA4, EGR3, EML6, EZH2, FADS3, FCER1G, FCRL2, FGL2, FLJ20373, FMOD, GADD45A, GLIPRI, GNB4, GPR160, GPR34, GRIK3, GUCD1, HCK, HIP1R, HIVEP3, HMCES, IGF2BP3, IGSF3, IL21R, INPP5F, IQGAP2, IQSEC1, ITGAX, ITGB5, JDP2, KANK2, KCNH2, KDM1B, KLF3, LATS2, LCN10, LEF1, LPL, LRRK2, LUZP1, MAP4K4, MID1IPI, MMP14, MPRIP, MSI2, MYBL1, MYL9, MYLIP, MZB1, NBPF3, NRIP1, NRSN2, NUGGC, NXPH4, P2RX1, P2RX5, P2RY14, PDGFD, PIP5K1B, PITPNC1, PON2, PRICKLE1, PTPN7, RCN3, RDX, RHBDF2, RIMKLB, RNF135, RP11-145M9.4, RP11-268J15.5, RP11-463012.3, RP5-1028K7.2, SAMSN1, SCCPDH, SCD, SCPEP1, SDC3, SECTM1, SESN3, SH3BP2, SH3D21, SLC16A5, SLC19A1, SLC4A7, SPN, SSBP3, STX5, SUSD1, TBC1D2B, TBC1D9, TBKBP1, TCF7, TFEC, TGFBR3, TIGIT, TIMELESS, TMEM133, TNFRSF13B, TOX2, TRAK2, TTC39C, TUBG2, VPS37B, VSIG10, WNT9A, ZAP70, ZNF667-AS1, ZNF804A, and ZSWIM6, or a subset thereof, as well as the nucleic acid molecules encoding such proteins. Fragments of the aforementioned polypeptides useful in the methods of the invention are sufficient to bind an antibody that specifically recognizes the protein from which the fragment is derived.

[0208] In some instances, markers useful for the panels of the invention include markers for U-CLL, namely XPO1, BCOR, KRAS, RPS23, RRM1, RAF1, MAP2K2, LRP1B, or a subset thereof, as well as the nucleic acid molecules encoding such proteins. In some cases, markers useful for the panels of the invention include markers for M-CLL, namely MYD88, KLHL6, ITPKB, TCL1A, DICER1, or a subset thereof, as well as the nucleic acid molecules encoding such proteins.

[0209] In embodiments, markers useful in the panels of the invention include markers for expression cluster Ec-i, namely, GRIK3, IQGAP2, FCER1G, STK32B, GADD45A, ITGAX, KLF3, RFTN1, PTK2, DFNB31, and ZMAT1, or a sub-set thereof, as well as the nucleic acid molecules encoding such proteins.

[0210] In embodiments, markers useful in the panels of the invention include markers for expression cluster EC-m1, namely, TFEC, COL18A1, SLC19A1, NRIP1, KCNH2, P2RX1, ARRDC5, BEX4, and APP, or a sub-set thereof, as well as the nucleic acid molecules encoding such proteins.

[0211] In embodiments, markers useful in the panels of the invention include markers for expression cluster EC-m2, namely, EML6, HCK, CD1C, VPS37B, CYBB, NXPH4, BTNL9, KLRK1, IQSEC1, BANKI, LEF1, SH3D21, FMOD, SEMA4A, CTLA4, ADTRP, IGSF3, IGFBP4, PDGFD, and APOD, or a sub-set thereof, as well as the nucleic acid molecules encoding such proteins.

[0212] In embodiments, markers useful in the panels of the invention include markers for expression cluster EC-m3, namely, MS4A4E, MYL9, NT5E, MS4A6A, PITPNC1, CNTNAP2, 5 IGF2BP3, WNT3, CLDN7, TCF7, BASP1, FLJ20373, MAP4K4, LRRK2, SAMSN1, CEACAM1, TNFRSF13B, PHF16, MID1IP1, and ABCA9, or a sub-set thereof, as well as the nucleic acid molecules encoding such proteins.

[0213] In embodiments, markers useful in the panels of the invention include markers for expression cluster EC-m4, namely, MYBL1, NUGGC, GNG8, AEBP1, HIP1R, LATS2, RIMKLB, EML6, FADS3, MBOAT1, LCN10, DCLK2, and GLUL, or a sub-set thereof, as well as the nucleic acid molecules encoding such proteins.

[0214] In embodiments, markers useful in the panels of the invention include markers for expression cluster EC-o, namely, ACSM3, TOX2, PHF16, SESN3, TBC1D9, PIP5KIB, SIK1, DUSP5, GNG7, HIVEP3, MARCKSL1, GPR183, HRK, and PITPNC1, or a sub-set thereof, as well as the nucleic acid molecules encoding such proteins.

[0215] In embodiments, markers useful in the panels of the invention include markers for expression cluster EC-ul, namely, SEPT10, LDOC1, LPL, KANK2, SOWAHC, DUSP26, OSBPL5, WNT9A, FGFR1, GTSF1L, ADD3, AKT3, COBLL1, MNDA, FCRL3, FAM49A, FCRL2, SLC2A3, and MARCKS, or a sub-set thereof, as well as the nucleic acid molecules encoding such proteins.

[0216] In embodiments, markers useful in the panels of the invention include markers for expression cluster EC-u2, namely, ITGB5, BCL7A, PPP1R9A, TSPAN13, SLC12A7, SSBP3, VASH1, SPG20, ILT3RA1, NR3C2, TUBG2, ZNF804A, and IL2RA, or a sub-set thereof, as well as the nucleic acid molecules encoding such proteins. The panels can comprise biomarkers for expression cluster Ec-i, EC-m1, EC-m2, EC-m3, EC-m4, EC-o, EC-ul, or EC-u2, or various combinations thereof.

[0217] The invention further features the use of such panels for characterizing chronic lymphocytic leukemia (CLL). In embodiments, the panels are used in combination with a classifier (e.g., a machine learning classifier) to identify a CLL as belonging to a particular expression subtype. The panels are advantageously used for guiding selection of a subject for a CLL treatment.

Biomarkers

[0218] Measurements of expression levels of biomarkers (e.g., polypeptide and/or polynucleotides encoding polypeptides present in expression clusters described herein) are used in combination with a model (e.g., a machine learning

classifier) to identify a chronic lymphocytic leukemia as belonging to a particular expression subtype. In particular embodiments, a biomarker is an organic biomolecule that is differentially present in a sample taken from a subject of one phenotypic status (e.g., having a disease, such as chronic lymphocytic leukemia (CLL)) as compared with another phenotypic status (e.g., not having the disease). A biomarker is differentially present between different phenotypic statuses if the mean or median expression level of the biomarker in the different groups is calculated to be statistically significant. Common tests for statistical significance include, among others, t-test, ANOVA, Kruskal-Wallis, Wilcoxon, Mann-Whitney and odds ratio. Biomarkers, alone or in combination, provide measures of relative risk that a subject belongs to one phenotypic status or another. Therefore, they are useful as markers for characterizing a disease (e.g., chronic lymphocytic leukemia (CLL)).

[0219] A biomarker of the invention may be detected in a biological sample of the subject (e.g., tissue, fluid), including, but not limited to blood, blood serum, plasma, saliva, urine, ascites, cyst fluid, a homogenized tissue sample (e.g., a tissue sample obtained by biopsy), a cell isolated from a patient sample, and the like.

[0220] The disclosure provides panels comprising isolated biomarkers. The biomarkers can be isolated from biological fluids. They can be isolated by any method known in the art. In certain embodiments, this isolation is accomplished using the mass and/or binding characteristics of the markers. For example, a sample comprising the biomolecules can be subject to chromatographic fractionation and subject to further separation by, e.g., acrylamide gel electrophoresis.

[0221] Knowledge of the identity of the biomarker also allows their isolation by immunoaffinity chromatography. In some embodiments, biomarkers described herein are fixed to a substrate (e.g., chips, beads, microfluidic platforms, membranes).

Detection of Biomarkers

[0222] The biomarkers of this disclosure can be detected by any suitable method. The methods described herein can be used individually or in combination for a more accurate detection of the biomarkers (e.g., biochip in combination with mass spectrometry, immunoassay in combination with mass spectrometry, and the like).

[0223] Detection paradigms that can be employed in the disclosure include, but are not limited to, optical methods, electrochemical methods (voltammetry and amperometry techniques), atomic force microscopy, and radio frequency methods, e.g., multipolar resonance spectroscopy.

[0224] Illustrative of optical methods, in addition to microscopy, both confocal and non-confocal, are detection of fluorescence, luminescence, chemiluminescence, absorbance, reflectance, transmittance, and birefringence or refractive index (e.g., surface plasmon resonance, ellipsometry, a resonant mirror method, a grating coupler waveguide method or interferometry).

[0225] These and additional methods are described below.

Detection by sequencing and/or probes

[0226] In particular embodiments, the biomarkers of the invention are measured by a sequencing- and/or probe-based technique (e.g., RNA-seq).

[0227] RNA sequencing (RNA-Seq) is a powerful tool for transcriptome profiling. In embodiments, to mitigate sequence-dependent bias resulting from amplification complications to allow truly digital RNA-Seq, a set of barcode sequences can be used to ensure that every cDNA molecule prepared from an mRNA sample is uniquely labeled by random attachment of barcode sequences to both ends (see, e.g., Shiroguchi K, et al. Proc Natl Acad Sci USA. 2012 Jan. 24;109(4):1347-52). After PCR, paired-end deep sequencing can be applied to read the two barcodes and cDNA sequences. Rather than counting the number of reads, RNA abundance can be measured based on the number of unique barcode sequences observed for a given cDNA sequence. The barcodes may be optimized to be unambiguously identifiable. This method is a representative example of how to quantify a whole transcriptome from a sample.

[0228] Detecting a target polynucleotide sequence or fragment thereof associated with a biomarker that hybridizes to a probe sequence may involve sequencing, FACS, qPCR, RT-PCR, a genotyping array, and/or a NanoString assay (see, e.g., Malkov, et al. "Multiplexed measurements of gene signatures in different analytes using the Nanostring nCounter™ Assay System", BMC Research Notes, 2: Article No: 80 (2009)), or any of various other techniques known to one of skill in the art. Various detection methods may be used and are described as follows.

[0229] Preparation of a library for sequencing may involve an amplification step. Amplification may involve thermocycling or isothermal amplification (such as through the methods RPA or LAMP). Cross-linking may involve overlap-extension PCR or use of ligase to associate multiple amplification products with each other. Amplification can refer to any method employing a primer and a polymerase capable of replicating a target sequence with reasonable fidelity. Amplification may be carried out by natural or recombinant DNA polymerases such as TaqGold™, T7 DNA polymerase, Klenow fragment of *E. coli* DNA polymerase, and reverse transcriptase. A preferred amplification method is PCR. In particular, the isolated RNA can be subjected to a reverse transcription assay that is coupled with a quantitative polymerase chain reaction (RT-PCR) in order to quantify the expression level of a biomarker.

[0230] Detection of the expression level of a biomarker can be conducted in real time in an amplification assay (e.g., qPCR). In one aspect, the amplified products can be directly visualized with fluorescent DNA-binding agents including but not limited to DNA intercalators and DNA groove binders. Because the amount of the intercalators incorporated into the double-stranded DNA molecules is typically proportional to the amount of the amplified DNA products, one can conveniently determine the amount of the amplified products by quantifying the fluorescence of the intercalated dye using conventional optical systems in the art. DNA-binding dyes suitable for this application include, as non-limiting examples, SYBR green, SYBR blue, DAPI, propidium iodine, Hoeste, SYBR gold, ethidium bromide, acridines, proflavine, acridine orange, acriflavine, fluorcoumanin, ellipticine, daunomycin, chloroquine, distamycin D, chromomycin, homidium, mithramycin, ruthenium polypyridyls, anthramycin, and the like.

[0231] Other fluorescent labels such as sequence specific probes can be employed in the amplification reaction to facilitate the detection and quantification of the amplified products. Probe-based quantitative amplification relies on the sequence-specific detection of a desired amplified product. It utilizes fluorescent, target-specific probes (e.g., TaqMan® probes) resulting in increased specificity and

sensitivity. Methods for performing probe-based quantitative amplification are taught, for example, in U.S. Pat. No. 5,210,015.

[0232] Sequencing may be performed on any high-throughput platform. Methods of sequencing oligonucleotides and nucleic acids are well known in the art (see, e.g., WO93/23564, WO98/28440 and WO98/13523; U.S. Pat. App. Pub. No. 2019/0078232; U.S. Pat. Nos. 5,525,464; 5,202,231; 5,695,940; 4,971,903; 5,902,723; 5,795,782; 5,547,839 and 5,403,708; Sanger et al., Proc. Natl. Acad. Sci. USA 74:5463 (1977); Drmanac et al., Genomics 4:114 (1989); Koster et al., Nature Biotechnology 14:1123 (1996); Hyman, Anal. Biochem. 174:423 (1988); Rosenthal, International Patent Application Publication 761107 (1989); Metzker et al., Nucl. Acids Res. 22:4259 (1994); Jones, Biotechniques 22:938 (1997); Ronaghi et al., Anal. Biochem. 242:84 (1996); Ronaghi et al., Science 281:363 (1998); Nyren et al., Anal. Biochem. 151:504 (1985); Canard and Arzumanov, Gene 11:1 (1994); Dyatkina and Arzumanov, Nucleic Acids Symp Ser 18:117 (1987); Johnson et al., Anal. Biochem. 136:192 (1984); and Elgen and Rigler, Proc. Natl. Acad. Sci. USA 91(13):5740 (1994), all of which are expressly incorporated by reference herein in their entirety).

[0233] The sequencing of a polynucleotide can be carried out using any suitable commercially available sequencing technology. In embodiments, the sequencing of a polynucleotide is carried out using a chain termination method of DNA sequencing (e.g., Sanger sequencing). In some embodiments, commercially available sequencing technology is a next-generation sequencing technology, including as non-limiting examples combinatorial probe anchor synthesis (cPAS), DNA nanoball sequencing, droplet-based or digital microfluidics, heliscope single molecule sequencing, nanopore sequencing (e.g., Oxford Nanopore technologies), GeneGap sequencing, massively parallel signature sequencing (MPSS), microfluidic Sanger sequencing, microscopy-based techniques (e.g., transmission electronic microscopy DNA sequencing), RNA polymerase (RNAP) sequencing, single-molecule real-time (SMRT) sequencing, SOLiD sequencing, ion semiconductor sequencing, polony sequencing, Pyrosequencing (454), sequencing by hybridization, sequencing by synthesis (e.g., Illumina™ sequencing), sequencing with mass spectrometry, and tunneling currents DNA sequencing.

[0234] In embodiments, levels of biomarkers in a sample are quantified using targeted sequencing. Methods for targeted sequencing are well known in the art (see, e.g., Rehm, "Disease-targeted sequencing: a cornerstone in the clinic", Nature Reviews Genetics, 14:295-300 (2013)).

[0235] In embodiments, a probe comprises a molecular identifier, such as a fluorescent or chemiluminescent label, a radioactive isotope label, an enzymatic ligand, or the like. The molecular identifier can be a fluorescent label or an enzyme tag, such as digoxigenin, (3-galactosidase, urease, alkaline phosphatase or peroxidase, avidin/biotin complex.

[0236] Methods used to detect or quantify binding of a probe to a target biomarker will typically depend upon the molecular identifier. For example, radiolabels may be detected using photographic film or a phosphoimager. Fluorescent markers may be detected and quantified using a photodetector to detect emitted light. Enzymatic labels can be detected by providing the enzyme with a substrate and measuring the reaction product produced by the action of the enzyme on the substrate; and colorimetric labels can be detected by visualizing a colored label.

[0237] Specific non-limiting examples of molecular identifiers include radioisotopes, such as 32P, 14C, 1251, 3H, and 1311, fluorescein, rhodamine, dansyl chloride, umbelliferone, luciferase, peroxidase, alkaline phosphatase, P-galactosidase, P-glucosidase, horseradish peroxidase, glucoamylase, lysozyme, saccharide oxidase, microperoxidase, biotin, and ruthenium. In the case where biotin is employed as a molecular identifier, streptavidin bound to an enzyme (e.g., peroxidase) may further be added to facilitate detection of the biotin.

[0238] Examples of fluorescent molecular identifiers include, but are not limited to, Atto dyes, 4-acetamido-4'-isothiocyanatostilbene-2,2' disulfonic acid; acridine and derivatives: acridine, acridine isothiocyanate; 5-(2'-aminoethyl)aminonaphthalene-1-sulfonic acid (EDANS); 4-amino-N-[3-vinyl sulfonyl)phenyl]naphthalimide-3,5 disulfonate; N-(4-anilino-1-naphthyl)maleimide; anthranilamide; BODIPY; Brilliant Yellow; coumarin and derivatives; coumarin, 7-amino-4-methylcoumarin (AMC, Coumarin 120), 7-amino-4-trifluoromethylcouluarin (Coumaran 151); cyanine dyes; cyanosine; 4',6-diaminidino-2-phenylindole (DAPI); 5'5"-dibromopyrogallol-sulfonaphthalein (Bromopyrogallol Red); 7-diethylamino-3-(4'-isothiocyanatophenyl)-4-methylcoumarin; diethylenetriamine pentaacetate; 4,4'-diisothiocyanatodihydro-stilbene-2,2'-disulfonic acid; 4,4'-diisothiocyanatostilbene-2,2'-disulfonic acid; 5-[dimethylamino]naphthalene-1-sulfonyl chloride (DNS, dansylchloride); 4-dimethylaminophenylazophenyl-4'-isothiocyanate (DABITC); eosin and derivatives; eosin, eosin isothiocyanate, erythrosin and derivatives; erythrosin B, erythrosin, isothiocyanate; ethidium; fluorescein and derivatives; 5-carboxyfluorescein (FAM), 5-(4,6-dichlorotriazin-2-yl)aminofluorescein (DTAF), 2',7'-dimethoxy-4'5'-dichloro-6-carboxyfluorescein, fluorescein, fluorescein isothiocyanate, QFITC, (XRITC); fluorescamine; IR144; IR1446; Malachite Green isothiocyanate; 4-methylumbelliferoneortho cresolphthalein; nitrotyrosine; pararosaniline; Phenol Red; B-phycoerythrin; o-phthaldialdehyde; pyrene and derivatives: pyrene, pyrene butyrate, succinimidyl 1-pyrene; butyrate quantum dots; Reactive Red 4 (Cibacron™ Brilliant Red 3B-A) rhodamine and derivatives: 6-carboxy-X-rhodamine (ROX), 6-carboxyrhodamine (R6G), lissamine rhodamine B sulfonyl chloride rhodamine (Rhod), rhodamine B, rhodamine 123, rhodamine X isothiocyanate, sulforhodamine B, sulforhodamine 101, sulfonyl chloride derivative of sulforhodamine 101 (Texas Red); N,N,N',N' tetramethyl-6-carboxyrhodamine (TAMRA); tetramethyl rhodamine; tetramethyl rhodamine isothiocyanate (TRITC); riboflavin; rosolic acid; terbium chelate derivatives; Cy3; Cy5; Cy5.5; Cy7; IRD 700; IRD 800; La Jolta Blue; phthalo cyanine; and naphthalo cyanine.

[0239] A fluorescent molecular identifier may be a fluorescent protein, such as blue fluorescent protein, cyan fluorescent protein, green fluorescent protein, red fluorescent protein, yellow fluorescent protein or any photoconvertible protein. Colorimetric molecular identifiers, bioluminescent molecular identifiers and/or chemiluminescent molecular identifiers may be used in embodiments of the disclosure.

[0240] Detection of a molecular identifier may involve detecting energy transfer between molecules in a hybridization complex by perturbation analysis, quenching, or elec-

tron transport between donor and acceptor molecules, the latter of which may be facilitated by double stranded match hybridization complexes. The fluorescent molecular identifier may be a perylene or a terrylen. In the alternative, the fluorescent molecular identifier may be a fluorescent bar code.

[0241] The molecular identifier may be light sensitive, wherein the label is light-activated and/or light cleaves the one or more linkers to release the molecular cargo. The light-activated molecular cargo may be a major light-harvesting complex (LHCII). In another embodiment, the fluorescent molecular label may induce free radical formation.

[0242] In an advantageous embodiment, agents may be uniquely labeled in a dynamic manner (see, e.g., international patent application serial no. PCT/US2013/61182 filed Sep. 23, 2012).

[0243] The unique labels are, at least in part, nucleic acid in nature, and may be generated by sequentially attaching two or more detectable oligonucleotide tags to each other and each unique label may be associated with a separate agent. A detectable oligonucleotide tag may be an oligonucleotide that may be detected by sequencing of its nucleotide sequence and/or by detecting non-nucleic acid detectable moieties to which it may be attached.

[0244] In embodiments, the molecular identifier is a microparticle, including, as non-limiting examples, quantum dots (Empodocles, et al., Nature 399:126-130, 1999), or gold nanoparticles (Reichert et al., Anal. Chem. 72:6025-6029, 2000).

Detection by Immunoassay

[0245] In particular embodiments, the biomarkers of the invention are measured by immunoassay. An immunoassay typically utilizes an antibody (or other agent that specifically binds the marker) to detect the presence or level of a biomarker in a sample. Antibodies can be produced by methods well known in the art, e.g., by immunizing animals with the biomarkers. Biomarkers can be isolated from samples based on their binding characteristics. Alternatively, if the amino acid sequence of a polypeptide biomarker is known, the polypeptide can be synthesized and used to generate antibodies by methods well known in the art.

[0246] This disclosure contemplates traditional immunoassays including, for example, Western blot, sandwich immunoassays including ELISA and other enzyme immunoassays, fluorescence-based immunoassays, and chemiluminescence. Nephelometry is an assay done in liquid phase, in which antibodies are in solution. Binding of the antigen to the antibody results in changes in absorbance, which is measured. Other forms of immunoassay include magnetic immunoassay, radioimmunoassay, and real-time immunoquantitative PCR (iqPCR).

[0247] Immunoassays can be carried out on solid substrates (e.g., chips, beads, microfluidic platforms, membranes) or on any other forms that supports binding of the antibody to the marker and subsequent detection. A single marker may be detected at a time or a multiplex format may be used. Multiplex immunoanalysis may involve planar microarrays (protein chips) and bead-based microarrays (suspension arrays).

[0248] In a SELDI-based immunoassay, a biospecific capture reagent for the biomarker is attached to the surface of an MS probe, such as a pre-activated ProteinChip array. The biomarker is then specifically captured on the biochip through this reagent, and the captured biomarker is detected by mass spectrometry.

Detection by Biochip

[0249] In embodiments, a sample is analyzed by means of a biochip (also known as a microarray). The polypeptides and nucleic acid molecules of the disclosure are useful as hybridizable array elements in a biochip. Biochips generally comprise solid substrates and have a generally planar surface, to which a capture reagent (also called an adsorbent or affinity reagent) is attached. Frequently, the surface of a biochip comprises a plurality of addressable locations, each of which has the capture reagent bound there.

[0250] The array elements are organized in an ordered fashion such that each element is present at a specified location on the substrate. Useful substrate materials include membranes, composed of paper, nylon or other materials, filters, chips, glass slides, and other solid supports. The ordered arrangement of the array elements allows hybridization patterns and intensities to be interpreted as expression levels of particular genes or proteins. Methods for making nucleic acid microarrays are known to the skilled artisan and are described, for example, in U.S. Pat. No. 5,837,832, Lockhart, et al. (Nat. Biotech. 14:1675-1680, 1996), and Schena, et al. (Proc. Natl. Acad. Sci. 93:10614-10619, 1996), herein incorporated by reference in its entrety. Methods for making polypeptide microarrays are described, for example, by Ge (Nucleic Acids Res. 28: e3. i-e3. vii, 2000), MacBeath et al., (Science 289:1760-1763, 2000), Zhu et al. (Nature Genet. 26:283-289), and in U.S. Pat. No. 6,436,665, hereby incorporated by reference in its entirety.

Detection by Protein Biochip

[0251] In embodiments, a sample is analyzed by means of a protein biochip (also known as a protein microarray). Such biochips are useful in high-throughput low-cost screens to identify alterations in the expression or post-translation modification of a biomarker, or a fragment thereof. In embodiments, a protein biochip of the disclosure binds a biomarker present in a sample and detects an alteration in the level of the biomarker. Typically, a protein biochip features a protein, or fragment thereof, bound to a solid support. Suitable solid supports include membranes (e.g., membranes composed of nitrocellulose, paper, or other material), polymer-based films (e.g., polystyrene), beads, or glass slides. For some applications, proteins (e.g., antibodies that bind a marker of the disclosure) are spotted on a substrate using any convenient method known to the skilled artisan (e.g., by hand or by inkjet printer).

[0252] In embodiments, the protein biochip is hybridized with a detectable probe. Such probes can be polypeptides, nucleic acid molecules, antibodies, or small molecules. For some applications, polypeptide and nucleic acid molecule probes are derived from a biological sample taken from a patient, such as a bodily fluid (such as blood, blood serum, plasma, saliva, urine, ascites, cyst fluid, and the like); a homogenized tissue sample (e.g., a tissue sample obtained by biopsy); or a cell isolated from a patient sample. Probes can also include antibodies, candidate peptides, nucleic acids, or small molecule compounds derived from a peptide, nucleic acid, or chemical library. Hybridization conditions (e.g., temperature, pH, protein concentration, and ionic

strength) are optimized to promote specific interactions. Such conditions are known to the skilled artisan and are described, for example, in Harlow, E. and Lane, D., Using Antibodies: A Laboratory Manual. 1998, New York: Cold Spring Harbor Laboratories. After removal of non-specific probes, specifically bound probes are detected, for example, by fluorescence, enzyme activity (e.g., an enzyme-linked calorimetric assay), direct immunoassay, radiometric assay, or any other suitable detectable method known to the skilled artisan.

[0253] Many protein biochips are described in the art. These include, for example, protein biochips produced by Ciphergen Biosystems, Inc. (Fremont, CA), Zyomyx (Hayward, CA), Packard BioScience Company (Meriden, CT), Phylos (Lexington, MA), Invitrogen (Carlsbad, CA), Biacore (Uppsala, Sweden) and Procognia (Berkshire, UK). Examples of such protein biochips are described in the following patents or published patent applications: U.S. Pat. Nos. 6,225,047; 6,537,749; 6,329,209; and 5,242,828; PCT International Publication Nos. WO 00/56934; WO 03/048768; and WO 99/51773.

Detection by Nucleic Acid Biochip

[0254] In aspects of the invention, a sample is analyzed by means of a nucleic acid biochip (also known as a nucleic acid microarray). To produce a nucleic acid biochip, oligonucleotides may be synthesized or bound to the surface of a substrate using a chemical coupling procedure and an ink jet application apparatus, as described in PCT application WO95/251116 (Baldeschweiler et al.). Alternatively, a gridded array may be used to arrange and link cDNA fragments or oligonucleotides to the surface of a substrate using a vacuum system, thermal, UV, mechanical or chemical bonding procedure.

[0255] A nucleic acid molecule (e.g. RNA or DNA) derived from a biological sample may be used to produce a hybridization probe as described herein. The biological samples are generally derived from a patient, e.g., as a bodily fluid (such as blood, blood serum, plasma, saliva, urine, ascites, cyst fluid, and the like); a homogenized tissue sample (e.g., a tissue sample obtained by biopsy); or a cell isolated from a patient sample. For some applications, cultured cells or other tissue preparations may be used. The mRNA is isolated according to standard methods, and cDNA is produced and used as a template to make complementary RNA suitable for hybridization. Such methods are well known in the art. The RNA is amplified in the presence of fluorescent nucleotides, and the labeled probes are then incubated with the microarray to allow the probe sequence to hybridize to complementary oligonucleotides bound to the biochip.

[0256] Incubation conditions are adjusted such that hybridization occurs with precise complementary matches or with various degrees of less complementarity depending on the degree of stringency employed, as defined above. The removal of nonhybridized probes may be accomplished, for example, by washing. The washing steps that follow hybridization can also vary in stringency, as defined above.

[0257] Detection systems for measuring the absence, presence, and amount of hybridization for all of the distinct nucleic acid sequences are well known in the art. For example, simultaneous detection is described in Heller et al., Proc. Natl. Acad. Sci. 94:2150-2155, 1997. In embodiments, a scanner is used to determine the levels and patterns of fluorescence.

Detection by Mass Spectrometry

[0258] In embodiments, the biomarkers of this disclosure are detected by mass spectrometry (MS). Mass spectrometry is a well-known tool for analyzing chemical compounds that employs a mass spectrometer to detect gas phase ions. Mass spectrometers are well known in the art and include, but are not limited to, time-of-flight, magnetic sector, quadrupole filter, ion trap, ion cyclotron resonance, electrostatic sector analyzer and hybrids of these. The method may be performed in an automated (Villanueva, et al., Nature Protocols (2006) 1(2):880-891) or semi-automated format. This can be accomplished, for example, with the mass spectrometer operably linked to a liquid chromatography device (LC-MS/MS or LC-MS) or gas chromatography device (GC-MS or GC-MS/MS). Methods for performing mass spectrometry are well known and have been disclosed, for example, in US Patent Application Publication Nos: 2005/0023454; 2005/0035286; U.S. Pat. No. 5,800,979 and the references disclosed therein.

Laser Desorption/Ionization

[0259] In embodiments, the mass spectrometer is a laser desorption/ionization mass spectrometer. In laser desorption/ionization mass spectrometry, the analytes are placed on the surface of a mass spectrometry probe, a device adapted to engage a probe interface of the mass spectrometer and to present an analyte to ionizing energy for ionization and introduction into a mass spectrometer. A laser desorption mass spectrometer employs laser energy, typically from an ultraviolet laser, but also from an infrared laser, to desorb analytes from a surface, to volatilize and ionize them and make them available to the ion optics of the mass spectrometer. The analysis of proteins by LDI can take the form of MALDI or of SELDI.

[0260] Laser desorption/ionization in a single time of flight instrument typically is performed in linear extraction mode. Tandem mass spectrometers can employ orthogonal extraction modes.

Matrix-assisted Laser Desorption/Ionization (MALDI) and Electrospray Ionization (ESI)

[0261] In embodiments, the mass spectrometric technique for use as disclosed herein is matrix-assisted laser desorption/ionization (MALDI) or electrospray ionization (ESI). In related embodiments, the procedure is MALDI with time of flight (TOF) analysis, known as MALDI-TOF MS. This involves forming a matrix on a membrane with an agent that absorbs the incident light strongly at the particular wavelength employed. The sample is excited by UV or IR laser light into the vapor phase in the MALDI mass spectrometer. Ions are generated by the vaporization and form an ion plume. The ions are accelerated in an electric field and separated according to their time of travel along a given distance, giving a mass/charge (m/z) reading which is very accurate and sensitive. MALDI spectrometers are well known in the art and are commercially available from, for example, PerSeptive Biosystems, Inc. (Framingham, Mass., USA).

[0262] Magnetic-based serum processing can be combined with traditional MALDI-TOF. Through this approach, improved peptide capture is achieved prior to matrix mixture and deposition of the sample on MALDI target plates. Accordingly, in embodiments, methods of peptide capture are enhanced through the use of derivatized magnetic bead based sample processing.

[0263] MALDI-TOF MS allows scanning of the fragments of many proteins at once. Thus, many proteins can be run simultaneously on a polyacrylamide gel, subjected to a method of the disclosure to produce an array of spots on a collecting membrane, and the array may be analyzed. Subsequently, automated output of the results is provided by using a server (e.g., ExPASy) to generate the data in a form suitable for computers.

[0264] Other techniques for improving the mass accuracy and sensitivity of the MALDI-TOF MS can be used to analyze the fragments of protein obtained on a collection membrane. These include, but are not limited to, the use of delayed ion extraction, energy reflectors, ion-trap modules, and the like. In addition, post source decay and MS-MS analysis are useful to provide further structural analysis. With ESI, the sample is in the liquid phase and the analysis can be by ion-trap, TOF, single quadrupole, multi-quadrupole mass spectrometers, and the like. The use of such devices (other than a single quadrupole) allows MS-MS or MS" analysis to be performed. Tandem mass spectrometry allows multiple reactions to be monitored at the same time.

[0265] Capillary infusion may be employed to introduce the biomarker to a desired mass spectrometer implementation, for instance, because it can efficiently introduce small quantities of a sample into a mass spectrometer without destroying the vacuum. Capillary columns are routinely used to interface the ionization source of a mass spectrometer with other separation techniques including, but not limited to, gas chromatography (GC) and liquid chromatography (LC). GC and LC can serve to separate a solution into its different components prior to mass analysis. Such techniques are readily combined with mass spectrometry. One variation of the technique is the coupling of high-performance liquid chromatography (HPLC) to a mass spectrometer for integrated sample separation/and mass spectrometer analysis.

[0266] Quadrupole mass analyzers may also be employed as needed to practice the disclosure. Fourier-transform ion cyclotron resonance (FTMS) can also be used for some embodiments. It offers high resolution and the ability of tandem mass spectrometry experiments. FTMS is based on the principle of a charged particle orbiting in the presence of a magnetic field. Coupled to ESI and MALDI, FTMS offers high accuracy with errors as low as 0.001%.

Surface-Enhanced Laser Desorption/Ionization (SELDI)

[0267] In embodiments, the mass spectrometric technique for use herein is "Surface Enhanced Laser Desorption and Ionization" or "SELDI," as described, for example, in U.S. Pat. Nos. 5,719,060; 6,225,047, both to Hutchens and Yip. This refers to a method of desorption/ionization gas phase ion spectrometry (e.g., mass spectrometry) in which an analyte (here, one or more of the biomarkers) is captured on the surface of a SELDI mass spectrometry probe.

[0268] SELDI has also been called "affinity capture mass spectrometry." It also is called "Surface-Enhanced Affinity Capture" or "SEAC". This version involves the use of probes that have a material on the probe surface that captures analytes through a non-covalent affinity interaction (adsorption) between the material and the analyte. The material is variously called an "adsorbent," a "capture reagent," an "affinity reagent" or a "binding moiety." Such probes can be referred to as "affinity capture probes" and as having an "adsorbent surface." The capture reagent can be any material capable of binding an analyte. The capture reagent is attached to the probe surface by physisorption or chemisorption. In certain embodiments, the probes have the capture reagent already attached to the surface. In other embodiments, the probes are pre-activated and include a reactive moiety that is capable of binding the capture reagent, e.g., through a reaction forming a covalent or coordinate covalent bond. Epoxide and acyl-imidizole are useful reactive moieties to covalently bind polypeptide capture reagents such as antibodies or cellular receptors. Nitrilotriacetic acid and iminodiacetic acid are useful reactive moieties that function as chelating agents to bind metal ions that interact non-covalently with histidine containing peptides. Adsorbents are generally classified as chromatographic adsorbents and biospecific adsorbents.

[0269] "Chromatographic adsorbent" refers to an adsorbent material typically used in chromatography. Chromatographic adsorbents include, for example, ion exchange materials, metal chelators (e.g., nitrilotriacetic acid or iminodiacetic acid), immobilized metal chelates, hydrophobic interaction adsorbents, hydrophilic interaction adsorbents, dyes, simple biomolecules (e.g., nucleotides, amino acids, simple sugars and fatty acids) and mixed mode adsorbents (e.g., hydrophobic attraction/electrostatic repulsion adsorbents).

[0270] A biospecific adsorbent is an adsorbent comprising a biomolecule, e.g., a nucleic acid molecule (e.g., an aptamer), a polypeptide, a polysaccharide, a lipid, a steroid or a conjugate of these (e.g., a glycoprotein, a lipoprotein, a glycolipid, a nucleic acid (e.g., DNA)-protein conjugate). In certain instances, the biospecific adsorbent can be a macromolecular structure such as a multiprotein complex, a biological membrane or a virus. Examples of biospecific adsorbents are antibodies, receptor proteins and nucleic acids. Biospecific adsorbents typically have higher specificity for a target analyte than chromatographic adsorbents. Further examples of adsorbents for use in SELDI can be found in U.S. Pat. No. 6,225,047. A "bioselective adsorbent" refers to an adsorbent that binds to an analyte with an affinity of at least 10^{-8} M.

[0271] Protein biochips produced by Ciphergen comprise surfaces having chromatographic or biospecific adsorbents attached thereto at addressable locations. Ciphergen's ProteinChip® arrays include NP20 (hydrophilic); H4 and H50 (hydrophobic); SAX-2, Q-10 and (anion exchange); WCX-2 and CM-10 (cation exchange); IMAC-3, IMAC-30 and IMAC-50 (metal chelate); and PS-10, PS-20 (reactive surface with acyl-imidazole, epoxide) and PG-20 (protein G coupled through acyl-imidazole). Hydrophobic ProteinChip arrays have isopropyl or nonylphenoxy-poly(ethylene glycol)methacrylate functionalities. Anion exchange ProteinChip arrays have quaternary ammonium functionalities. Cation exchange ProteinChip arrays have carboxylate functionalities. Immobilized metal chelate ProteinChip arrays have nitrilotriacetic acid functionalities (IMAC 3 and IMAC 30) or O-methacryloyl-N,N-bis-carboxymethyl tyrosine functionalities (IMAC 50) that adsorb transition metal ions,

such as copper, nickel, zinc, and gallium, by chelation. Preactivated ProteinChip arrays have acyl-imidazole or epoxide functional groups that can react with groups on proteins for covalent binding.

[0272] Such biochips are further described in: U.S. Pat. No. 6,579,719 (Hutchens and Yip, "Retentate Chromatography," Jun. 17, 2003); U.S. Pat. No. 6,897,072 (Rich et al., "Probes for a Gas Phase Ion Spectrometer," May 24, 2005); U.S. Pat. No. 6,555,813 (Beecher et al., "Sample Holder with Hydrophobic Coating for Gas Phase Mass Spectrometer," Apr. 29, 2003); U.S. Patent Application Publication No. U.S. 2003/0032043 A1 (Pohl and Papanu, "Latex Based Adsorbent Chip," Jul. 16, 2002); and PCT International Publication No. WO 03/040700 (Um et al., "Hydrophobic Surface Chip," May 15, 2003); U.S. Patent Application Publication No. US 2003/0218130 A1 (Boschetti et al., "Biochips With Surfaces Coated With Polysaccharide-Based Hydrogels," Apr. 14, 2003) and U.S. Pat. No. 7,045,366 (Huang et al., "Photocrosslinked Hydrogel Blend Surface Coatings" May 16, 2006).

[0273] In general, a probe with an adsorbent surface is contacted with the sample for a period of time sufficient to allow the biomarker or biomarkers that may be present in the sample to bind to the adsorbent. After an incubation period, the substrate is washed to remove unbound material. Any suitable washing solutions can be used; preferably, aqueous solutions are employed. The extent to which molecules remain bound can be manipulated by adjusting the stringency of the wash. The elution characteristics of a wash solution can depend, for example, on pH, ionic strength, hydrophobicity, degree of chaotropism, detergent strength, and temperature. Unless the probe has both SEAC and SEND properties (as described herein), an energy absorbing molecule then is applied to the substrate with the bound biomarkers.

[0274] In yet another method, one can capture the biomarkers with a solid-phase bound immuno-adsorbent that has antibodies that bind the biomarkers. After washing the adsorbent to remove unbound material, the biomarkers are eluted from the solid phase and detected by applying to a SELDI biochip that binds the biomarkers and analyzing by SELDI.

[0275] The biomarkers bound to the substrates are detected in a gas phase ion spectrometer such as a time-of-flight mass spectrometer. The biomarkers are ionized by an ionization source such as a laser, the generated ions are collected by an ion optic assembly, and then a mass analyzer disperses and analyzes the passing ions. The detector then translates information of the detected ions into mass-to-charge ratios. Detection of a biomarker typically will involve detection of signal intensity. Thus, both the quantity and mass of the biomarker can be determined.

Classification Algorithms

[0276] The present disclosure provides methods for characterizing a chronic lymphocytic leukemia (CLL) as belonging to an expression subtype (e.g., Ec-i, EC-m1, EC-m2, EC-m3, EC-m4, EC-o, EC-ul, and EC-u2). The expression subtype is useful in predicting clinical outcome for a CLL patient and/or for guiding therapy.

[0277] In some embodiments, data derived from the assays for detection of biomarkers (e.g., RNA-seq) that are generated using samples such as "known samples" can then be used to "train" a classification model. Exemplary methods for developing a model for classifying a chronic lymphocytic leukemia as belonging to an expression subtype are described in the Examples provided herein. A "known sample" is a sample that has been pre-classified. The data used to form the classification model can be referred to as a "training data set." Once trained, the classification model (e.g., a machine learning classifier) can be used to classify the expression subtype of a chronic lymphocytic leukemia (CLL) based upon levels of biomarkers detected in a sample. The sample can be taken from a subject having CLL. This can be useful, for example, in guiding selection of a treatment for a subject or for prognostic purposes.

[0278] The training data set that is used to form the classification model may comprise raw data or pre-processed data. In embodiments, a classifier can be trained using a random forest classifier, as described in the Examples provided herein.

[0279] Classification models can be formed using any suitable statistical classification (or "learning") method that attempts to segregate bodies of data into classes based on objective parameters present in the data. Classification methods may be either supervised or unsupervised. Examples of supervised and unsupervised classification processes are described in Jain, "Statistical Pattern Recognition: A Review", IEEE Transactions on Pattern Analysis and Machine Intelligence, Vol. 22, No. 1, January 2000, the teachings of which are incorporated by reference herein in their entirety.

[0280] In supervised classification, training data containing examples of known categories are presented to a learning mechanism, which learns one or more sets of relationships that define each of the known classes. New data may then be applied to the learning mechanism, which then classifies the new data using the learned relationships. Examples of supervised classification processes include linear regression processes (e.g., multiple linear regression (MLR), partial least squares (PLS) regression and principal components regression (PCR)), binary decision trees (e.g., recursive partitioning processes such as CART—classification and regression trees), artificial neural networks such as back propagation networks, discriminant analyses (e.g., Bayesian classifier or Fischer analysis), logistic classifiers, and support vector classifiers (support vector machines).

[0281] In embodiments, a supervised classification method is a recursive partitioning process. Recursive partitioning processes use recursive partitioning trees to classify data derived from unknown samples. Further details about recursive partitioning processes are provided in U.S. Patent Application Publication No. 2002/0138208 A1 to Paulse et al., "Method for analyzing mass spectra."

[0282] In embodiments, the classification models that are created can be formed using unsupervised learning methods. Unsupervised classification attempts to learn classifications based on similarities in the training data set, without pre-classifying the spectra from which the training data set was derived. Unsupervised learning methods include cluster analyses. A cluster analysis attempts to divide the data into "clusters" or groups that ideally should have members that are very similar to each other, and very dissimilar to members of other clusters. Similarity is then measured using some distance metric, which measures the distance between data items, and clusters together data items that are closer to

each other. Clustering techniques include the MacQueen's K-means algorithm and the Kohonen's Self-Organizing Map algorithm.

[0283] Learning algorithms asserted for use in classifying biological information are described, for example, in PCT International Publication No. WO 01/31580 (Barnhill et al., "Methods and devices for identifying patterns in biological systems and methods of use thereof"), U.S. Patent Application Publication No. 2002/0193950 A1 (Gavin et al., "Method or analyzing mass spectra"), U.S. Patent Application Publication No. 2003 0004402 A1 (Hitt et al., "Process for discriminating between biological states based on hidden patterns from biological data"), and U.S. Patent Application Publication No. 2003/0055615 A1 (Zhang and Zhang, "Systems and methods for processing biological expression data").

[0284] The classification models can be formed on and used on any suitable digital computer. Suitable digital computers include micro, mini, or large computers using any standard or specialized operating system, such as a Unix, Windows® or Linux® based operating system. The digital computer that is used may be physically separate from a device that is used to detect biomarkers, or it may be coupled to the device.

[0285] The training data set and the classification models according to embodiments of the invention can be embodied by computer code that is executed or used by a digital computer. The computer code can be stored on any suitable computer readable media including optical or magnetic disks, sticks, tapes, etc., and can be written in any suitable computer programming language including C, C++, visual basic, etc.

Hardware and Software

[0286] The present invention also provides a computer system useful in analyzing data associated with biomarker expression, patient selection, and related computations (e.g., calculations associated with a machine learning classifier).

[0287] A computer system (or digital device) may be used to receive, transmit, display and/or store results, analyze the results, and/or produce a report of the results and analysis. A computer system may be understood as a logical apparatus that can read instructions from media (e.g. software) and/or network port (e.g. from the internet), which can optionally be connected to a server having fixed media. A computer system may comprise one or more of a CPU, disk drives, input devices such as keyboard and/or mouse, and a display (e.g. a monitor). Data communication, such as transmission of instructions or reports, can be achieved through a communication medium to a server at a local or a remote location. The communication medium can include any means of transmitting and/or receiving data. For example, the communication medium can be a network connection, a wireless connection, or an internet connection. Such a connection can provide for communication over the World Wide Web. It is envisioned that data relating to the present invention can be transmitted over such networks or connections (or any other suitable means for transmitting information, including but not limited to mailing a physical report, such as a print-out) for reception and/or for review by a receiver. One can record results of calculations (e.g., sequence analysis or a listing of hybrid capture probe sequences) made by a computer on tangible medium, for example, in computer-readable format such as a memory drive or disk, as an output displayed on a computer monitor or other monitor, or simply printed on paper. The results can be reported on a computer screen. The receiver can be but is not limited to an individual, or electronic system (e.g. one or more computers, and/or one or more servers).

[0288] In some embodiments, the computer system may comprise one or more processors. Processors may be associated with one or more controllers, calculation units, and/or other units of a computer system, or implanted in firmware as desired. If implemented in software, the routines may be stored in any computer readable memory such as in RAM, ROM, flash memory, a magnetic disk, a laser disk, or other suitable storage medium. Likewise, this software may be delivered to a computing device via any known delivery method including, for example, over a communication channel such as a telephone line, the internet, a wireless connection, etc., or via a transportable medium, such as a computer readable disk, flash drive, etc. The various steps may be implemented as various blocks, operations, tools, modules and techniques which, in turn, may be implemented in hardware, firmware, software, or any combination of hardware, firmware, and/or software. When implemented in hardware, some or all of the blocks, operations, techniques, etc. may be implemented in, for example, a custom integrated circuit (IC), an application specific integrated circuit (ASIC), a field programmable logic array (FPGA), a programmable logic array (PLA), etc.

[0289] A client-server, relational database architecture can be used in embodiments of the invention. A client-server architecture is a network architecture in which each computer or processor on the network is either a client or a server. Server computers are typically powerful computers dedicated to managing disk drives (file servers), printers (print servers), or network traffic (network servers). Client computers include PCs (personal computers) or workstations on which users run applications, as well as example output devices as disclosed herein. Client computers rely on server computers for resources, such as files, devices, and even processing power. In some embodiments of the invention, the server computer handles all of the database functionality. The client computer can have software that handles all the front-end data management and can also receive data input from users.

[0290] A machine readable medium that may comprise computer-executable code may take many forms, including but not limited to, a tangible storage medium, a carrier wave medium or physical transmission medium. Non-volatile storage media include, for example, optical or magnetic disks, such as any of the storage devices in any computer(s) or the like, such as may be used to implement the databases, etc. shown in the drawings. Volatile storage media include dynamic memory, such as main memory of such a computer platform. Tangible transmission media include coaxial cables; copper wire and fiber optics, including the wires that comprise a bus within a computer system. Carrier-wave transmission media may take the form of electric or electromagnetic signals, or acoustic or light waves such as those generated during radio frequency (RF) and infrared (IR) data communications. Common forms of computer-readable media therefore include for example: a floppy disk, a flexible disk, hard disk, magnetic tape, any other magnetic medium, a CD-ROM, DVD or DVD-ROM, any other optical medium, punch cards paper tape, any other physical storage medium with patterns of holes, a RAM, a ROM, a PROM

and EPROM, a FLASH-EPROM, any other memory chip or cartridge, a carrier wave transporting data or instructions, cables or links transporting such a carrier wave, or any other medium from which a computer may read programming code and/or data. Many of these forms of computer readable media may be involved in carrying one or more sequences of one or more instructions to a processor for execution.

[0291] The subject computer-executable code can be executed on any suitable device which may comprise a processor, including a server, a PC, or a mobile device such as a smartphone or tablet. Any controller or computer optionally includes a monitor, which can be a cathode ray tube ("CRT") display, a flat panel display (e.g., active matrix liquid crystal display, liquid crystal display, etc.), or others. Computer circuitry is often placed in a box, which includes numerous integrated circuit chips, such as a microprocessor, memory, interface circuits, and others. The box also optionally includes a hard disk drive, a floppy disk drive, a high capacity removable drive such as a writeable CD-ROM, and other common peripheral elements. Inputting devices such as a keyboard, mouse, or touch-sensitive screen, optionally provide for input from a user.

[0292] The computer can include appropriate software for receiving user instructions, either in the form of user input into a set of parameter fields, e.g., in a GUI, or in the form of preprogrammed instructions, e.g., preprogrammed for a variety of different specific operations.

Pharmaceutical Compositions

[0293] As reported herein, the panels of biomarkers presented herein can be used in a method to select a subject for treatment with an agent. In embodiments, the treatment is administered as part of a clinical trial. Accordingly, the disclosure provides chemotherapeutic compositions for treatment of chronic lymphocytic leukemia (CLL). Non-limiting examples of agents suitable for use in the methods provided herein include those listed in Tables 1A and 1B or otherwise listed herein. The compositions should be sterile and contain a therapeutically effective amount of the polypeptides or nucleic acid molecules in a unit of weight or volume suitable for administration to a subject.

[0294] In embodiments, the composition contains a drug selected from one of those listed in Tables 1A and 1B below, and the like (e.g., alternative drugs effective in the treatment of chronic lymphocytic leukemia (CLL)). In embodiments, the drug has the same main target, or the same target category (A) or (B) as a drug listed in Tables 1A and 1B.

TABLE 1A

Agents for treatment of CLL.

drug_name	drug_name_alias	drug_category	target_category	main_targets
A-1331852		BH3 mimetic	Apoptosis (BH3)	BCL-XL
Abexinostat		HDAC inhibitor	Epigenetics	pan-HDAC (mostly HDAC1)
Acalabrutinib	ACP-196	BTK inhibitor	B cell receptor signaling	BTK
Atorvastatin		Statin	Antilipemic	HMG-COA
Azacitidine		DNA methylation inhibitor	Epigenetics	
AZD5991		BH3 mimetic	Apoptosis (BH3)	MCL1
AZD8055		mTOR inhibitor	mTOR signaling	mTOR
Bendamustine		DNA alkylator	DNA damage response	DNA
Carfilzomib	PR-171	Proteasome inhibitor	Proteasome	
Cerdulatinib	PRT062070	SYK and JAK/STAT inhibitor	BCR and JAK/STAT signaling	JAK1, JAK2, JAK3, SYK, TYK2
Crizotinib	PF-02341066	ALK inhibitor	ALK/MET/ROS	ALK, c-Met/HGF, ROS
Dasatinib	BMS-354825	BCR/ABL inhibitor	BCR-ABL	BCR-ABL, SRC
Duvelisib	IPI-145	PI3K inhibitor	PI3K/AKT signaling	PI3K
Entospletinib	GS-9973	SYK inhibitor	B cell receptor signaling	SYK
Erastin		Ferroptosis inducer	Ferroptosis	VDAC
Fludarabine	NSC 118218	Antimetabolite	DNA synthesis	
Gandotinib	LY2784544	JAK/STAT inhibitor	JAK/STAT signaling	JAK2, FLT3, FLT4, FGFR2, TYK2, TRKB
GSK690693		PI3K/AKT/mTOR inhibitor	PI3K/AKT signaling	AKT1, AKT2, AKT3
Ibrutinib	PCI-32765	BTK inhibitor	B cell receptor signaling	BTK
Idelalisib	CAL-101	PI3K inhibitor	PI3K/AKT signaling	PI3K
JQ1		Bromodomain inhibitor	Epigenetics	BET bromodomain inhibitor
Lenalidomide	CC-5013	Immunomodulatory drug (IMiD)	Immunomodulati on	IKZF1, IKZF3
MK-2206	MK2206	AKT inhibitor	PI3K/AKT signaling	AKT1, AKT2, AKT3

TABLE 1A-continued

Agents for treatment of CLL.

drug__name	drug__name__alias	drug__category	target__category	main__targets
Navitoclax	ABT-263	BH3 mimetic	Apoptosis (BH3)	BCL-XL, BCL-2 and BCL-W
Nirogacestat	PF-3084014	γ-secretase inhibitor	NOTCH signaling	γ-secretase
Nutlin-3		MDM2 inhibitor	DNA damage response	MDM2
Onalespib	AT13387	HSP90 inhibitor	Heat shock protein	HSP90
Osimertinib	AZD9291	EGFR inhibitor	EGFR signaling	EGFR (mutated)
Ponatinib	AP24534	BCR-ABL inhibitor	BCR-ABL	BCR-ABL, PDGFR, VEGFR, FGFR, SRC
Rapamycin	AY-22989	mTOR inhibitor	mTOR signaling	mTORC1, FKBP12
Ricolinostat	ACY-1215	HDAC inhibitor	Epigenetics	HDAC6 (less: HDAC1, HDAC2, HDAC3)
Ruxolitinib	INCB18424	JAK/STAT inhibitor	JAK/STAT signaling	JAK1, JAK2
Selinexor	KPT-330	XPO1 inhibitor	Nuclear export	XPO1
Sorafenib	BAY-43-9006	MAPK inhibitor	MAPK signaling	RAF, PDGF, VEGFR2, VEGFR3, KIT
Sunitinib	SU-11248	VEGF inhibitor	VEGF signaling	
Trametinib	GSK1120212	MAPK inhibitor	MAPK signaling	MEK1, MEK2
Umbralisib	TGR1202	PI3K inhibitor	PI3K/AKT signaling	PI3Kδ
Vecabrutinib	SNS-062	BTK inhibitor	B cell receptor signaling	
Venetoclax	ABT-199	BH3 mimetic	Apoptosis (BH3)	BCL2
Vorinostat	MK0683	HDAC inhibitor	Epigenetics	
Voruciclib	NSC-3590	CDK inhibitor	Cell cycle control	CDK9, MCL1, CDK4/6, CDK1
Zanubrutinib	BGB-3111	BTK inhibitor	B cell receptor signaling	BTK

TABLE 1B

Agents for treatment of CLL.

	Drug	Target
1	Idelalisib (CAL-101)	PI3K-delta
2	Duvelisib (IPI-145)	PI3K-delta, gamma
3	Umbralisib	PI3K-d
4	Gandotinib	JAK2
5	Trametinib	MEK1/MEK2
6	Sorafenib	BRAF
7	Rapamycin	mTOR
8	AZD8055	mTOR
9	MK2206	AKT
10	Acalabrutinib	BTK
11	SNS-062	BTK
12	Entosplentinib	SYK
13	Cerdulatinib	JAK/SYK
14	Crizotinib	ALK
15	Dasatinib	Abl
16	Ponatinib	TK
17	Ruxolitinib	JAK1/2
18	Voruciclib	CDK9
19	Sunitinib	RTK
20	Carfilzomib	Proteosome
21	Lenalidomide	Immunomodulator
22	Fludarabine	DNA damaging agent
23	Bendamustine	Alkylating agent
24	Azacitidine	DNA methylating agent
25	Nutlin-3	MDM2
26	Abexinostat	HDAC
27	Vorinostat	HDAC

TABLE 1B-continued

Agents for treatment of CLL.

	Drug	Target
28	Ricolinostat	selective HDAC 6
29	JQ1	Bromodomain
30	ABT-263	BCL-2/BCL-XL/BCLw
31	AZD5991	MCL-1
32	A-1331852	BCL-xl
33	Erastin	Ferroptosis inducer
34	Atoruvastatin	HMG-CoA reductase
35	Onalespib	HSP90
36	PF-3084014	gamma-secretase
37	GSK690396	AKT
38	Selinexor	Nuclear export
39	Venetoclax	BCL2
40	Ibrutinib	BTK
41	AZD9291	EGFR
42	Zanabrutinib	BTK

TABLE 2

Gene Drivers and their Sensitivity to CLL Treatment Agents

peptide	drug	feature	dprim__pearson__corr	direction
PUMA 1 uM	A-1331852	loss__6q21	−0.5859268	Resistant

TABLE 2-continued

Gene Drivers and their Sensitivity to CLL Treatment Agents

peptide	drug	feature	dprim_pearson_corr	direction
PUMA 1 uM	A-1331852	CNOT3	0.4470944	Sensitive
PUMA 1 uM	A-1331852	EC-m2	−0.3621573	Resistant
PUMA 1 uM	AZD5991	EC-i	0.45349954	Sensitive
PUMA 1 uM	AZD5991	BIRC3	0.4088154	Sensitive
PUMA 1 uM	AZD5991	loss_7p22.2	0.44897072	Sensitive
PUMA 1 uM	AZD5991	loss_16p11.2	0.37742434	Sensitive
PUMA 1 uM	AZD5991	loss_17q11.2	0.4088154	Sensitive
PUMA 1 uM	AZD5991	loss_1q42.13	0.35362592	Sensitive
PUMA 1 uM	AZD5991	loss_9p21.3	0.4088154	Sensitive
PUMA 1 uM	Abexinostat	loss_17q23.1	0.33522272	Sensitive
PUMA 1 uM	Abexinostat	loss_6q21	0.3538112	Sensitive
PUMA 1 uM	Abexinostat	EC-m2	0.45571182	Sensitive
PUMA 1 uM	Atorvastatin	RFX7	−0.3377731	Resistant
PUMA 1 uM	Atorvastatin	FBXW7	−0.3807836	Resistant
PUMA 1 uM	Atorvastatin	loss_2q31.1	−0.3576906	Resistant
PUMA 1 uM	Atorvastatin	ZMYM3	−0.3377731	Resistant
PUMA 1 uM	Atorvastatin	loss_7p22.2	−0.3484779	Resistant
PUMA 1 uM	Atorvastatin	gain_16p11.2	−0.3743338	Resistant
PUMA 1 uM	Atorvastatin	loss_10p12.2	−0.3576906	Resistant
PUMA 1 uM	Azacitidine	CARD11	0.50143359	Sensitive
PUMA 1 uM	Bendamustine	loss_14q32.12	0.33413206	Sensitive
PUMA 1 uM	Bendamustine	gain_7q22.1	0.36184927	Sensitive
PUMA 1 uM	Carfilzomib	i-CLL	0.43213969	Sensitive
PUMA 1 uM	Carfilzomib	loss_3p21.31	0.35409837	Sensitive
PUMA 1 uM	Carfilzomib	loss_14q32.12	0.35409837	Sensitive
PUMA 1 uM	Carfilzomib	gain_7q22.1	0.47287271	Sensitive
PUMA 1 uM	Carfilzomib	MYD88	0.44097787	Sensitive
PUMA 1 uM	Cerdulatinib	loss_13q14.3	0.33070389	Sensitive
PUMA 1 uM	Cerdulatinib	loss_13q14.13	0.45233099	Sensitive
PUMA 1 uM	Crizotinib	EC-i	−0.3956383	Resistant
PUMA 1 uM	Crizotinib	NOTCH1	−0.3508287	Resistant
PUMA 1 uM	Crizotinib	IGLV321_R110	−0.3508287	Resistant
PUMA 1 uM	Crizotinib	loss_6q	−0.3508287	Resistant
PUMA 1 uM	Crizotinib	RPS15	−0.3508287	Resistant
PUMA 1 uM	Dasatinib	NOTCH1	−0.478335	Resistant
PUMA 1 uM	Dasatinib	IGLV321_R110	−0.478335	Resistant

TABLE 2-continued

Gene Drivers and their Sensitivity to CLL Treatment Agents

peptide	drug	feature	dprim_pearson_corr	direction
PUMA 1 uM	Dasatinib	loss_17q23.1	0.35195754	Sensitive
PUMA 1 uM	Dasatinib	loss_6q	−0.478335	Resistant
PUMA 1 uM	Dasatinib	RPS15	−0.478335	Resistant
PUMA 1 uM	Duvelisib	loss_17q23.1	0.34171963	Sensitive
PUMA 1 uM	Duvelisib	loss_17p13.1	0.34171963	Sensitive
PUMA 1 uM	Duvelisib	EC-m2	0.3945238	Sensitive
PUMA 1 uM	Entospletinib	loss_19p13.11	0.40294784	Sensitive
PUMA 1 uM	Erastin	loss_8p	−0.4591263	Resistant
PUMA 1 uM	Erastin	EC-m3	−0.3301407	Resistant
PUMA 1 uM	Erastin	EC-i	−0.3373168	Resistant
PUMA 1 uM	Erastin	loss_7q36.1	−0.4591263	Resistant
PUMA 1 uM	GSK690693	i-CLL	0.41029257	Sensitive
PUMA 1 uM	GSK690693	BIRC3	0.43691279	Sensitive
PUMA 1 uM	GSK690693	ITIH2	0.43691279	Sensitive
PUMA 1 uM	GSK690693	loss_17q11.2	0.43691279	Sensitive
PUMA 1 uM	GSK690693	loss_9p21.3	0.43691279	Sensitive
PUMA 1 uM	Gandotinib	EC-i	−0.3507015	Resistant
PUMA 1 uM	Gandotinib	GNB1	0.33399627	Sensitive
PUMA 1 uM	Ibrutinib	loss_6q21	−0.5196509	Resistant
PUMA 1 uM	Idelalisib	DICER1	−0.3326945	Resistant
PUMA 1 uM	Idelalisib	MED1	−0.3326945	Resistant
PUMA 1 uM	Idelalisib	EC-m4	0.34331218	Sensitive
PUMA 1 uM	Idelalisib	KMT2D	0.3371123	Sensitive
PUMA 1 uM	JQ1	loss_8p	−0.6160372	Resistant
PUMA 1 uM	JQ1	EC-i	−0.5959866	Resistant
PUMA 1 uM	JQ1	loss_1q21.3	−0.3770763	Resistant
PUMA 1 uM	JQ1	loss_12p13.31a	−0.5064866	Resistant
PUMA 1 uM	JQ1	loss_18q21.2	0.33831656	Sensitive
PUMA 1 uM	JQ1	loss_5p15.33	−0.5064866	Resistant
PUMA 1 uM	JQ1	loss_2q31.1	−0.4197346	Resistant
PUMA 1 uM	JQ1	loss_3p13	0.36761499	Sensitive
PUMA 1 uM	JQ1	loss_16q22.1	−0.373144	Resistant
PUMA 1 uM	JQ1	ATM	−0.4530874	Resistant
PUMA 1 uM	JQ1	loss_7p22.2	−0.3770763	Resistant
PUMA 1 uM	JQ1	gain_16p11.2	−0.390517	Resistant
PUMA 1 uM	JQ1	loss_10q24.32	0.33831656	Sensitive

TABLE 2-continued

Gene Drivers and their Sensitivity to CLL Treatment Agents

peptide	drug	feature	dprim_pearson_corr	direction
PUMA 1 uM	JQ1	loss_3p21.31	−0.6160372	Resistant
PUMA 1 uM	JQ1	loss_14q32.12	−0.6160372	Resistant
PUMA 1 uM	JQ1	loss_10p12.2	−0.4197346	Resistant
PUMA 1 uM	JQ1	loss_1p36.11	0.33831656	Sensitive
PUMA 1 uM	JQ1	loss_7q36.1	−0.6160372	Resistant
PUMA 1 uM	JQ1	MYD88	−0.6160372	Resistant
PUMA 1 uM	JQ1	loss_17p13.3	−0.5064866	Resistant
PUMA 1 uM	MK-2206	priortrt_Post	−0.3482936	Resistant
PUMA 1 uM	Navitoclax	EC-m4	0.33245488	Sensitive
PUMA 1 uM	Navitoclax	loss_6q21	−0.5997546	Resistant
PUMA 1 uM	Navitoclax	loss_14q32.12	0.35735421	Sensitive
PUMA 1 uM	Navitoclax	EC-m2	−0.4445467	Resistant
PUMA 1 uM	Nirogacestat	BIRC3	0.4303189	Sensitive
PUMA 1 uM	Nirogacestat	loss_1q21.3	0.33363306	Sensitive
PUMA 1 uM	Nirogacestat	loss_7p22.2	0.36058747	Sensitive
PUMA 1 uM	Nirogacestat	loss_17q11.2	0.4303189	Sensitive
PUMA 1 uM	Nirogacestat	loss_9p21.3	0.4303189	Sensitive
PUMA 1 uM	Nutlin-3	priortrt_Post	−0.4306035	Resistant
PUMA 1 uM	Nutlin-3	FBXW7	−0.3313826	Resistant
PUMA 1 uM	Nutlin-3	EC-m4	0.3496268	Sensitive
PUMA 1 uM	Nutlin-3	loss_17p13.1	−0.3687944	Resistant
PUMA 1 uM	Onalespib	loss_6q21	−0.5471562	Resistant
PUMA 1 uM	Osimertinib	BIRC3	0.38799985	Sensitive
PUMA 1 uM	Osimertinib	loss_3p21.31	−0.3558358	Resistant
PUMA 1 uM	Osimertinib	loss_17q11.2	0.38799985	Sensitive
PUMA 1 uM	Osimertinib	loss_9p21.3	0.38799985	Sensitive
PUMA 1 uM	Osimertinib	MYD88	−0.4725921	Resistant
PUMA 1 uM	Ponatinib	RFX7	−0.4213822	Resistant
PUMA 1 uM	Ponatinib	priortrt_Post	−0.5032364	Resistant
PUMA 1 uM	Ponatinib	loss_2q31.1	−0.3631316	Resistant
PUMA 1 uM	Ponatinib	ZMYM3	−0.4213822	Resistant
PUMA 1 uM	Ponatinib	loss_10p12.2	−0.3631316	Resistant
PUMA 1 uM	Ponatinib	m-CLL	0.41758483	Sensitive
PUMA 1 uM	Rapamycin	RFX7	−0.5651278	Resistant
PUMA 1 uM	Rapamycin	EC-u1	−0.4444035	Resistant
PUMA 1 uM	Rapamycin	i-CLL	0.46970843	Sensitive

TABLE 2-continued

Gene Drivers and their Sensitivity to CLL Treatment Agents

peptide	drug	feature	dprim_pearson_corr	direction
PUMA 1 uM	Rapamycin	priortrt_Post	−0.3633407	Resistant
PUMA 1 uM	Rapamycin	U-CLL	−0.4657341	Resistant
PUMA 1 uM	Rapamycin	EC-m4	0.41842197	Sensitive
PUMA 1 uM	Rapamycin	ZMYM3	−0.5651278	Resistant
PUMA 1 uM	Rapamycin	n-CLL	−0.4739873	Resistant
PUMA 1 uM	Rapamycin	M-CLL	0.46573411	Sensitive
PUMA 1 uM	Ricolinostat	loss_15q15.1b	−0.3847567	Resistant
PUMA 1 uM	Ricolinostat	i-CLL	−0.3930618	Resistant
PUMA 1 uM	Ricolinostat	loss_1q21.3	−0.3766571	Resistant
PUMA 1 uM	Ricolinostat	loss_12p13.31a	−0.3467068	Resistant
PUMA 1 uM	Ricolinostat	loss_5p15.33	−0.3467068	Resistant
PUMA 1 uM	Ricolinostat	loss_2q31.1	−0.3442189	Resistant
PUMA 1 uM	Ricolinostat	CARD11	0.34960477	Sensitive
PUMA 1 uM	Ricolinostat	loss_16q22.1	−0.3467068	Resistant
PUMA 1 uM	Ricolinostat	loss_7p22.2	−0.3766571	Resistant
PUMA 1 uM	Ricolinostat	gain_16p11.2	−0.4183658	Resistant
PUMA 1 uM	Ricolinostat	loss_3p21.31	−0.4057486	Resistant
PUMA 1 uM	Ricolinostat	loss_14q32.12	−0.4057486	Resistant
PUMA 1 uM	Ricolinostat	loss_10p12.2	−0.3442189	Resistant
PUMA 1 uM	Ricolinostat	loss_20p11.22	−0.3847567	Resistant
PUMA 1 uM	Ricolinostat	m-CLL	0.38059876	Sensitive
PUMA 1 uM	Ricolinostat	loss_17p13.3	−0.3467068	Resistant
PUMA 1 uM	Ruxolitinib	U-CLL	−0.3389186	Resistant
PUMA 1 uM	Ruxolitinib	loss_11q22.3	−0.3372231	Resistant
PUMA 1 uM	Ruxolitinib	n-CLL	−0.3553018	Resistant
PUMA 1 uM	Ruxolitinib	M-CLL	0.33891856	Sensitive
PUMA 1 uM	Selinexor	loss_8p	0.35546713	Sensitive
PUMA 1 uM	Selinexor	loss_7q36.1	0.35546713	Sensitive
PUMA 1 uM	Sorafenib	RFX7	−0.5439862	Resistant
PUMA 1 uM	Sorafenib	FBXW7	−0.3983393	Resistant
PUMA 1 uM	Sorafenib	ZMYM3	−0.5439862	Resistant
PUMA 1 uM	Sunitinib	gain_19p13.3	−0.3705342	Resistant
PUMA 1 uM	Sunitinib	RFX7	−0.5237902	Resistant
PUMA 1 uM	Sunitinib	FBXW7	−0.4644002	Resistant
PUMA 1 uM	Sunitinib	loss_2q31.1	−0.3637593	Resistant
PUMA 1 uM	Sunitinib	ZMYM3	−0.5237902	Resistant

TABLE 2-continued

Gene Drivers and their Sensitivity to CLL Treatment Agents

peptide	drug	feature	dprim_pearson_corr	direction
PUMA 1 uM	Sunitinib	loss_10p12.2	−0.3637593	Resistant
PUMA 1 uM	Trametinib	CHD2	0.53055601	Sensitive
PUMA 1 uM	Trametinib	TP53	0.37315291	Sensitive
PUMA 1 uM	Trametinib	EC-m1	−0.3588799	Resistant
PUMA 1 uM	Trametinib	CUL9	−0.353067	Resistant
PUMA 1 uM	Umbralisib	NOTCH1	−0.3958792	Resistant
PUMA 1 uM	Umbralisib	IGLV321_R110	−0.3960778	Resistant
PUMA 1 uM	Umbralisib	loss_12p13.31a	0.38748565	Sensitive
PUMA 1 uM	Umbralisib	U-CLL	−0.4629576	Resistant
PUMA 1 uM	Umbralisib	loss_5p15.33	0.38748565	Sensitive
PUMA 1 uM	Umbralisib	n-CLL	−0.3356869	Resistant
PUMA 1 uM	Umbralisib	loss_6q	−0.3960778	Resistant
PUMA 1 uM	Umbralisib	M-CLL	0.46295764	Sensitive
PUMA 1 uM	Umbralisib	RPS15	−0.3960778	Resistant
PUMA 1 uM	Venetoclax	loss_6q21	−0.6708865	Resistant
PUMA 1 uM	Venetoclax	EC-m2	−0.5106933	Resistant
PUMA 1 uM	Vorinostat	i-CLL	−0.3317217	Resistant
PUMA 1 uM	Vorinostat	loss_6q21	0.336181	Sensitive
PUMA 1 uM	Vorinostat	EC-m2	0.3339204	Sensitive
PUMA 1 uM	Voruciclib	i-CLL	0.37258884	Sensitive
PUMA 1 uM	Voruciclib	SF3B1	−0.3336378	Resistant
PUMA 1 uM	Zanubrutinib	gain_19p13.3	−0.3860208	Resistant
PUMA 1 uM	Zanubrutinib	BIRC3	−0.5322225	Resistant
PUMA 1 uM	Zanubrutinib	loss_1q21.3	−0.3844555	Resistant
PUMA 1 uM	Zanubrutinib	FBXW7	−0.3945898	Resistant
PUMA 1 uM	Zanubrutinib	ITIH2	−0.5322225	Resistant
PUMA 1 uM	Zanubrutinib	loss_7p22.2	−0.3844555	Resistant
PUMA 1 uM	Zanubrutinib	gain_16p11.2	−0.4882074	Resistant
PUMA 1 uM	Zanubrutinib	loss_17p13.1	−0.5322225	Resistant
PUMA 1 uM	Zanubrutinib	loss_17q11.2	−0.5322225	Resistant
PUMA 1 uM	Zanubrutinib	loss_9p21.3	−0.5322225	Resistant
MS1 2.5 uM	AZD5991	CNOT3	0.75935526	Sensitive
MS1 2.5 uM	AZD8055	NOTCH1	−0.3618136	Resistant
MS1 2.5 uM	AZD8055	IGLV321_R110	−0.3618136	Resistant
MS1 2.5 uM	AZD8055	loss_18q21.2	−0.3305838	Resistant
MS1 2.5 uM	AZD8055	loss_3p13	−0.3305838	Resistant

TABLE 2-continued

Gene Drivers and their Sensitivity to CLL Treatment Agents

peptide	drug	feature	dprim_pearson_corr	direction
MS1 2.5 uM	AZD8055	loss_6q	−0.3618136	Resistant
MS1 2.5 uM	AZD8055	loss_1p36.11	−0.3305838	Resistant
MS1 2.5 uM	AZD8055	RPS15	−0.3618136	Resistant
MS1 2.5 uM	Abexinostat	priortrt_Post	0.35791198	Sensitive
MS1 2.5 uM	Abexinostat	FBXW7	0.3832463	Sensitive
MS1 2.5 uM	Abexinostat	ITIH2	0.34485221	Sensitive
MS1 2.5 uM	Atorvastatin	RFX7	−0.8667203	Resistant
MS1 2.5 uM	Atorvastatin	loss_11q22.3	−0.4356328	Resistant
MS1 2.5 uM	Atorvastatin	loss_10q24.2	−0.5072844	Resistant
MS1 2.5 uM	Atorvastatin	loss_2q31.1	−0.4261955	Resistant
MS1 2.5 uM	Atorvastatin	ZMYM3	−0.8667203	Resistant
MS1 2.5 uM	Atorvastatin	n-CLL	−0.3847935	Resistant
MS1 2.5 uM	Atorvastatin	loss_10p12.2	−0.4261955	Resistant
MS1 2.5 uM	Azacitidine	BIRC3	0.44950434	Sensitive
MS1 2.5 uM	Azacitidine	ITIH2	0.44950434	Sensitive
MS1 2.5 uM	Azacitidine	loss_19p13.11	0.33873888	Sensitive
MS1 2.5 uM	Azacitidine	loss_17q11.2	0.44950434	Sensitive
MS1 2.5 uM	Azacitidine	loss_9p21.3	0.44950434	Sensitive
MS1 2.5 uM	Bendamustine	BIRC3	0.43549527	Sensitive
MS1 2.5 uM	Bendamustine	CNOT3	0.70329503	Sensitive
MS1 2.5 uM	Bendamustine	loss_17q11.2	0.43549527	Sensitive
MS1 2.5 uM	Bendamustine	loss_9p21.3	0.43549527	Sensitive
MS1 2.5 uM	Cerdulatinib	loss_13q14.13	0.36118573	Sensitive
MS1 2.5 uM	Crizotinib	RFX7	−0.5099227	Resistant
MS1 2.5 uM	Crizotinib	NOTCH1	−0.3921101	Resistant
MS1 2.5 uM	Crizotinib	IGLV321_R110	−0.3921101	Resistant
MS1 2.5 uM	Crizotinib	priortrt_Post	−0.3729429	Resistant
MS1 2.5 uM	Crizotinib	ZMYM3	−0.5099227	Resistant
MS1 2.5 uM	Crizotinib	loss_6q	−0.3921101	Resistant
MS1 2.5 uM	Crizotinib	RPS15	−0.3921101	Resistant
MS1 2.5 uM	Dasatinib	EC-i	−0.4190906	Resistant
MS1 2.5 uM	Dasatinib	NOTCH1	−0.6405408	Resistant
MS1 2.5 uM	Dasatinib	IGLV321_R110	−0.6405408	Resistant
MS1 2.5 uM	Dasatinib	loss_6q	−0.6405408	Resistant
MS1 2.5 uM	Dasatinib	tri_12	0.39018403	Sensitive
MS1 2.5 uM	Dasatinib	RPS15	−0.6405408	Resistant

TABLE 2-continued

Gene Drivers and their Sensitivity to CLL Treatment Agents

peptide	drug	feature	dprim_pearson_corr	direction
MS1 2.5 uM	Duvelisib	loss_17q23.1	0.35409209	Sensitive
MS1 2.5 uM	Duvelisib	loss_17p13.1	0.35409209	Sensitive
MS1 2.5 uM	Entospletinib	loss_19p13.11	0.33669984	Sensitive
MS1 2.5 uM	Fludarabine	BIRC3	0.44305439	Sensitive
MS1 2.5 uM	Fludarabine	ITIH2	0.50360592	Sensitive
MS1 2.5 uM	Fludarabine	loss_17q11.2	0.44305439	Sensitive
MS1 2.5 uM	Fludarabine	loss_9p21.3	0.44305439	Sensitive
MS1 2.5 uM	GSK690693	EC-m3	−0.3847545	Resistant
MS1 2.5 uM	GSK690693	i-CLL	0.40885601	Sensitive
MS1 2.5 uM	GSK690693	loss_13q14.13	0.37283349	Sensitive
MS1 2.5 uM	GSK690693	EC-o	0.33701895	Sensitive
MS1 2.5 uM	Ibrutinib	loss_19p13.11	0.43395101	Sensitive
MS1 2.5 uM	Idelalisib	tri_12	0.38216015	Sensitive
MS1 2.5 uM	JQ1	EC-m4	0.39012985	Sensitive
MS1 2.5 uM	Lenalidomide	CNOT3	0.33071669	Sensitive
MS1 2.5 uM	MK-2206	EC-i	−0.4274473	Resistant
MS1 2.5 uM	MK-2206	IGLV321_R110	−0.5268628	Resistant
MS1 2.5 uM	MK-2206	loss_6q	−0.5268628	Resistant
MS1 2.5 uM	MK-2206	RPS15	−0.5268628	Resistant
MS1 2.5 uM	Navitoclax	loss_8p	0.42290643	Sensitive
MS1 2.5 uM	Navitoclax	gain_16p11.2	0.3378385	Sensitive
MS1 2.5 uM	Navitoclax	loss_3p21.31	0.48327152	Sensitive
MS1 2.5 uM	Navitoclax	loss_14q32.12	0.36089533	Sensitive
MS1 2.5 uM	Navitoclax	loss_7q36.1	0.42290643	Sensitive
MS1 2.5 uM	Navitoclax	MYD88	0.4615326	Sensitive
MS1 2.5 uM	Nutlin-3	EC-m4	0.33733821	Sensitive
MS1 2.5 uM	Onalespib	loss_19p13.11	0.4067422	Sensitive
MS1 2.5 uM	Osimertinib	EC-i	−0.3441832	Resistant
MS1 2.5 uM	Osimertinib	NOTCH1	−0.4871931	Resistant
MS1 2.5 uM	Osimertinib	IGLV321_R110	−0.4871931	Resistant
MS1 2.5 uM	Osimertinib	loss_6q	−0.4871931	Resistant
MS1 2.5 uM	Osimertinib	RPS15	−0.4871931	Resistant
MS1 2.5 uM	Ponatinib	RFX7	−0.7386591	Resistant
MS1 2.5 uM	Ponatinib	NOTCH1	−0.4169651	Resistant
MS1 2.5 uM	Ponatinib	IGLV321_R110	−0.4169651	Resistant
MS1 2.5 uM	Ponatinib	priortrt_Post	−0.4869062	Resistant

TABLE 2-continued

Gene Drivers and their Sensitivity to CLL Treatment Agents

peptide	drug	feature	dprim_pearson_corr	direction
MS1 2.5 uM	Ponatinib	FBXW7	−0.3833616	Resistant
MS1 2.5 uM	Ponatinib	loss_10q24.2	−0.5360884	Resistant
MS1 2.5 uM	Ponatinib	loss_2q31.1	−0.431849	Resistant
MS1 2.5 uM	Ponatinib	ZMYM3	−0.7386591	Resistant
MS1 2.5 uM	Ponatinib	loss_6q	−0.4169651	Resistant
MS1 2.5 uM	Ponatinib	loss_10p12.2	−0.431849	Resistant
MS1 2.5 uM	Ponatinib	RPS15	−0.4169651	Resistant
MS1 2.5 uM	Rapamycin	RFX7	−0.6708833	Resistant
MS1 2.5 uM	Rapamycin	EC-u1	−0.4081365	Resistant
MS1 2.5 uM	Rapamycin	priortrt_Post	−0.5247781	Resistant
MS1 2.5 uM	Rapamycin	U-CLL	−0.4001589	Resistant
MS1 2.5 uM	Rapamycin	FBXW7	−0.3836273	Resistant
MS1 2.5 uM	Rapamycin	loss_11q22.3	−0.3838154	Resistant
MS1 2.5 uM	Rapamycin	loss_10q24.2	−0.4815459	Resistant
MS1 2.5 uM	Rapamycin	loss_2q31.1	−0.3824336	Resistant
MS1 2.5 uM	Rapamycin	ZMYM3	−0.6708833	Resistant
MS1 2.5 uM	Rapamycin	n-CLL	−0.5147572	Resistant
MS1 2.5 uM	Rapamycin	M-CLL	0.4001589	Sensitive
MS1 2.5 uM	Rapamycin	loss_10p12.2	−0.3824336	Resistant
MS1 2.5 uM	Ricolinostat	CNOT3	0.46109945	Sensitive
MS1 2.5 uM	Ricolinostat	loss_10q24.32	−0.3885268	Resistant
MS1 2.5 uM	Ricolinostat	m-CLL	0.39146931	Sensitive
MS1 2.5 uM	Ruxolitinib	NOTCH1	−0.4522592	Resistant
MS1 2.5 uM	Ruxolitinib	IGLV321_R110	−0.4522592	Resistant
MS1 2.5 uM	Ruxolitinib	loss_6q	−0.4522592	Resistant
MS1 2.5 uM	Ruxolitinib	RPS15	−0.4522592	Resistant
MS1 2.5 uM	Sorafenib	gain_19p13.3	−0.4424339	Resistant
MS1 2.5 uM	Sorafenib	RFX7	−0.8770851	Resistant
MS1 2.5 uM	Sorafenib	priortrt_Post	−0.5222341	Resistant
MS1 2.5 uM	Sorafenib	loss_11q22.3	−0.434434	Resistant
MS1 2.5 uM	Sorafenib	loss_10q24.2	−0.5202678	Resistant
MS1 2.5 uM	Sorafenib	loss_2q31.1	−0.4677062	Resistant
MS1 2.5 uM	Sorafenib	ZMYM3	−0.8770851	Resistant
MS1 2.5 uM	Sorafenib	loss_10p12.2	−0.4677062	Resistant
MS1 2.5 uM	Sorafenib	m-CLL	0.34460982	Sensitive
MS1 2.5 uM	Sunitinib	RFX7	−0.6585943	Resistant

TABLE 2-continued

Gene Drivers and their Sensitivity to CLL Treatment Agents

peptide	drug	feature	dprim_pearson_corr	direction
MS1 2.5 uM	Sunitinib	priortrt_Post	−0.4090967	Resistant
MS1 2.5 uM	Sunitinib	U-CLL	−0.3746284	Resistant
MS1 2.5 uM	Sunitinib	FBXW7	−0.3482133	Resistant
MS1 2.5 uM	Sunitinib	loss_10q24.2	−0.3670408	Resistant
MS1 2.5 uM	Sunitinib	loss_2q31.1	−0.3521378	Resistant
MS1 2.5 uM	Sunitinib	ZMYM3	−0.6585943	Resistant
MS1 2.5 uM	Sunitinib	n-CLL	−0.3690725	Resistant
MS1 2.5 uM	Sunitinib	M-CLL	0.37462839	Sensitive
MS1 2.5 uM	Sunitinib	loss_10p12.2	−0.3521378	Resistant
MS1 2.5 uM	Trametinib	CHD2	0.3824262	Sensitive
MS1 2.5 uM	Trametinib	EC-i	−0.4494912	Resistant
MS1 2.5 uM	Trametinib	NOTCH1	−0.4082263	Resistant
MS1 2.5 uM	Trametinib	IGLV321_R110	−0.5391527	Resistant
MS1 2.5 uM	Trametinib	loss_6q	−0.5391527	Resistant
MS1 2.5 uM	Trametinib	RPS15	−0.5391527	Resistant
MS1 2.5 uM	Umbralisib	EC-i	−0.346901	Resistant
MS1 2.5 uM	Umbralisib	NOTCH1	−0.3542668	Resistant
MS1 2.5 uM	Umbralisib	IGLV321_R110	−0.4531376	Resistant
MS1 2.5 uM	Umbralisib	U-CLL	−0.3532312	Resistant
MS1 2.5 uM	Umbralisib	loss_6q	−0.4531376	Resistant
MS1 2.5 uM	Umbralisib	M-CLL	0.35323115	Sensitive
MS1 2.5 uM	Umbralisib	gain_7q22.1	0.40480838	Sensitive
MS1 2.5 uM	Umbralisib	RPS15	−0.4531376	Resistant
MS1 2.5 uM	Venetoclax	POT1	0.34442157	Sensitive
MS1 2.5 uM	Venetoclax	loss_13q14.13	0.34896275	Sensitive
MS1 2.5 uM	Venetoclax	gain_16p11.2	0.3631573	Sensitive
MS1 2.5 uM	Voruciclib	SAMHD1	−0.3336984	Resistant
MS1 2.5 uM	Zanubrutinib	gain_19p13.3	−0.3488323	Resistant
MS1 2.5 uM	Zanubrutinib	RFX7	−0.4526979	Resistant
MS1 2.5 uM	Zanubrutinib	FBXW7	−0.37558	Resistant
MS1 2.5 uM	Zanubrutinib	ZMYM3	−0.4526979	Resistant
BAD 0.3 uM	A-1331852	CNOT3	0.38194078	Sensitive
BAD 0.3 uM	AZD5991	EC-i	0.37911078	Sensitive
BAD 0.3 uM	AZD5991	POT1	0.42166522	Sensitive
BAD 0.3 uM	AZD5991	loss_7p22.2	0.330507	Sensitive
BAD 0.3 uM	AZD5991	loss_14q32.12	0.40648567	Sensitive

TABLE 2-continued

Gene Drivers and their Sensitivity to CLL Treatment Agents

peptide	drug	feature	dprim_pearson_corr	direction
BAD 0.3 uM	AZD5991	loss_16p11.2	0.55266804	Sensitive
BAD 0.3 uM	AZD5991	loss_1q42.13	0.53341994	Sensitive
BAD 0.3 uM	Abexinostat	EC-m2	0.39731553	Sensitive
BAD 0.3 uM	Atorvastatin	gain_19p13.3	0.35935709	Sensitive
BAD 0.3 uM	Atorvastatin	RFX7	0.49701967	Sensitive
BAD 0.3 uM	Atorvastatin	EC-u1	0.42618459	Sensitive
BAD 0.3 uM	Atorvastatin	U-CLL	0.35026526	Sensitive
BAD 0.3 uM	Atorvastatin	FBXW7	0.40543892	Sensitive
BAD 0.3 uM	Atorvastatin	ZMYM3	0.49701967	Sensitive
BAD 0.3 uM	Atorvastatin	n-CLL	0.39787953	Sensitive
BAD 0.3 uM	Atorvastatin	M-CLL	−0.3502653	Resistant
BAD 0.3 uM	Atorvastatin	m-CLL	−0.420056	Resistant
BAD 0.3 uM	Azacitidine	loss_19p13.11	0.39193137	Sensitive
BAD 0.3 uM	Azacitidine	CARD11	0.47557006	Sensitive
BAD 0.3 uM	Azacitidine	MYD88	0.38614039	Sensitive
BAD 0.3 uM	Bendamustine	EC-i	0.36174873	Sensitive
BAD 0.3 uM	Bendamustine	loss_12p13.31a	0.36311374	Sensitive
BAD 0.3 uM	Bendamustine	loss_5p15.33	0.36311374	Sensitive
BAD 0.3 uM	Bendamustine	loss_7p22.2	0.37937529	Sensitive
BAD 0.3 uM	Bendamustine	loss_14q32.12	0.4636513	Sensitive
BAD 0.3 uM	Bendamustine	loss_16p11.2	0.61602839	Sensitive
BAD 0.3 uM	Bendamustine	loss_1q42.13	0.45587516	Sensitive
BAD 0.3 uM	Cerdulatinib	loss_13q14.3	0.48803187	Sensitive
BAD 0.3 uM	Cerdulatinib	loss_13q14.13	0.44644712	Sensitive
BAD 0.3 uM	Crizotinib	RFX7	0.55715299	Sensitive
BAD 0.3 uM	Crizotinib	EC-i	−0.3482038	Resistant
BAD 0.3 uM	Crizotinib	EC-u1	0.37851483	Sensitive
BAD 0.3 uM	Crizotinib	NOTCH1	−0.3688823	Resistant
BAD 0.3 uM	Crizotinib	IGLV321_R110	−0.3688823	Resistant
BAD 0.3 uM	Crizotinib	loss_11q22.3	0.36905109	Sensitive
BAD 0.3 uM	Crizotinib	ZMYM3	0.55715299	Sensitive
BAD 0.3 uM	Crizotinib	n-CLL	0.39436071	Sensitive
BAD 0.3 uM	Crizotinib	loss_6q	−0.3688823	Resistant
BAD 0.3 uM	Crizotinib	RPS15	−0.3688823	Resistant
BAD 0.3 uM	Dasatinib	NOTCH1	−0.5130779	Resistant
BAD 0.3 uM	Dasatinib	IGLV321_R110	−0.5130779	Resistant

TABLE 2-continued

Gene Drivers and their Sensitivity to CLL Treatment Agents

peptide	drug	feature	dprim_pearson_corr	direction
BAD 0.3 uM	Dasatinib	loss_6q	−0.5130779	Resistant
BAD 0.3 uM	Dasatinib	RPS15	−0.5130779	Resistant
BAD 0.3 uM	Duvelisib	loss_17q23.1	0.37806892	Sensitive
BAD 0.3 uM	Duvelisib	loss_17p13.1	0.37806892	Sensitive
BAD 0.3 uM	Entospletinib	loss_17q23.1	0.35991923	Sensitive
BAD 0.3 uM	Entospletinib	loss_19p13.11	0.47996356	Sensitive
BAD 0.3 uM	Entospletinib	loss_17p13.1	0.37235435	Sensitive
BAD 0.3 uM	Erastin	EC-i	−0.3447734	Resistant
BAD 0.3 uM	GSK690693	POT1	−0.3915694	Resistant
BAD 0.3 uM	GSK690693	loss_3p13	−0.3480723	Resistant
BAD 0.3 uM	GSK690693	EC-o	0.36161943	Sensitive
BAD 0.3 uM	Gandotinib	EC-i	−0.4144924	Resistant
BAD 0.3 uM	Gandotinib	GNB1	0.33154559	Sensitive
BAD 0.3 uM	JQ1	loss_8p	−0.3437573	Resistant
BAD 0.3 uM	JQ1	gain_19p13.3	0.35896456	Sensitive
BAD 0.3 uM	JQ1	i-CLL	0.33271819	Sensitive
BAD 0.3 uM	JQ1	BIRC3	0.63547763	Sensitive
BAD 0.3 uM	JQ1	loss_12p13.31a	−0.3995505	Resistant
BAD 0.3 uM	JQ1	FBXW7	0.5086376	Sensitive
BAD 0.3 uM	JQ1	ITIH2	0.63547763	Sensitive
BAD 0.3 uM	JQ1	loss_5p15.33	−0.3995505	Resistant
BAD 0.3 uM	JQ1	loss_3p21.31	−0.3437573	Resistant
BAD 0.3 uM	JQ1	loss_17p13.1	0.50698974	Sensitive
BAD 0.3 uM	JQ1	loss_14q32.12	−0.3437573	Resistant
BAD 0.3 uM	JQ1	loss_7q36.1	−0.3437573	Resistant
BAD 0.3 uM	JQ1	EC-m2	0.38769258	Sensitive
BAD 0.3 uM	JQ1	loss_17q11.2	0.63547763	Sensitive
BAD 0.3 uM	JQ	loss_9p21.3	0.63547763	Sensitive
BAD 0.3 uM	JQ1	MYD88	−0.3437573	Resistant
BAD 0.3 uM	JQ1	loss_17p13.3	−0.3995505	Resistant
BAD 0.3 uM	Lenalidomide	loss_10q24.32	−0.354437	Resistant
BAD 0.3 uM	MK-2206	EC-i	−0.4300923	Resistant
BAD 0.3 uM	MK-2206	IGLV321_R110	−0.4533833	Resistant
BAD 0.3 uM	MK-2206	priortrt_Post	−0.3325602	Resistant
BAD 0.3 uM	MK-2206	loss_6q	−0.4533833	Resistant
BAD 0.3 uM	MK-2206	RPS15	−0.4533833	Resistant

TABLE 2-continued

Gene Drivers and their Sensitivity to CLL Treatment Agents

peptide	drug	feature	dprim_pearson_corr	direction
BAD 0.3 uM	Navitoclax	loss_8p	0.34214958	Sensitive
BAD 0.3 uM	Navitoclax	EC-m3	0.33802914	Sensitive
BAD 0.3 uM	Navitoclax	EC-u1	−0.3717303	Resistant
BAD 0.3 uM	Navitoclax	loss_12p13.31a	0.33632285	Sensitive
BAD 0.3 uM	Navitoclax	U-CLL	−0.4616729	Resistant
BAD 0.3 uM	Navitoclax	loss_5p15.33	0.33632285	Sensitive
BAD 0.3 uM	Navitoclax	n-CLL	−0.4049764	Resistant
BAD 0.3 uM	Navitoclax	loss_3p21.31	0.39049159	Sensitive
BAD 0.3 uM	Navitoclax	loss_14q32.12	0.45889323	Sensitive
BAD 0.3 uM	Navitoclax	M-CLL	0.46167289	Sensitive
BAD 0.3 uM	Navitoclax	loss_7q36.1	0.34214958	Sensitive
BAD 0.3 uM	Navitoclax	loss_17p13.3	0.33632285	Sensitive
BAD 0.3 uM	Nirogacestat	loss_18q21.2	−0.3785608	Resistant
BAD 0.3 uM	Nirogacestat	loss_3p13	−0.356381	Resistant
BAD 0.3 uM	Nirogacestat	loss_1p36.11	−0.3785608	Resistant
BAD 0.3 uM	Nutlin-3	priortrt_Post	−0.416614	Resistant
BAD 0.3 uM	Nutlin-3	U-CLL	−0.4093096	Resistant
BAD 0.3 uM	Nutlin-3	M-CLL	0.40930963	Sensitive
BAD 0.3 uM	Onalespib	loss_13q14.13	0.35335742	Sensitive
BAD 0.3 uM	Onalespib	loss_16p11.2	0.39143469	Sensitive
BAD 0.3 uM	Onalespib	loss_1q42.13	0.35967286	Sensitive
BAD 0.3 uM	Osimertinib	NOTCH1	−0.362555	Resistant
BAD 0.3 uM	Osimertinib	IGLV321_R110	−0.362555	Resistant
BAD 0.3 uM	Osimertinib	loss_6q	−0.362555	Resistant
BAD 0.3 uM	Osimertinib	RPS15	−0.362555	Resistant
BAD 0.3 uM	Osimertinib	MYD88	−0.4311851	Resistant
BAD 0.3 uM	Ponatinib	RFX7	0.38527486	Sensitive
BAD 0.3 uM	Ponatinib	EC-i	−0.3953926	Resistant
BAD 0.3 uM	Ponatinib	NOTCH1	−0.3559831	Resistant
BAD 0.3 uM	Ponatinib	IGLV321_R110	−0.3559831	Resistant
BAD 0.3 uM	Ponatinib	i-CLL	−0.447291	Resistant
BAD 0.3 uM	Ponatinib	ZMYM3	0.38527486	Sensitive
BAD 0.3 uM	Ponatinib	loss_3p13	−0.3534033	Resistant
BAD 0.3 uM	Ponatinib	loss_6q	−0.3559831	Resistant
BAD 0.3 uM	Ponatinib	RPS15	−0.3559831	Resistant
BAD 0.3 uM	Ponatinib	m-CLL	0.35855774	Sensitive

TABLE 2-continued

Gene Drivers and their Sensitivity to CLL Treatment Agents

peptide	drug	feature	dprim_pearson_corr	direction
BAD 0.3 uM	Rapamycin	RFX7	−0.5061225	Resistant
BAD 0.3 uM	Rapamycin	EC-u1	−0.3689429	Resistant
BAD 0.3 uM	Rapamycin	priortrt_Post	−0.4255941	Resistant
BAD 0.3 uM	Rapamycin	U-CLL	−0.3794115	Resistant
BAD 0.3 uM	Rapamycin	FBXW7	−0.4413568	Resistant
BAD 0.3 uM	Rapamycin	loss_11q22.3	−0.3321682	Resistant
BAD 0.3 uM	Rapamycin	ZMYM3	−0.5061225	Resistant
BAD 0.3 uM	Rapamycin	n-CLL	−0.4134887	Resistant
BAD 0.3 uM	Rapamycin	M-CLL	0.37941148	Sensitive
BAD 0.3 uM	Ricolinostat	CARD11	0.33195138	Sensitive
BAD 0.3 uM	Ruxolitinib	ITIH2	−0.3811264	Resistant
BAD 0.3 uM	Ruxolitinib	loss_13q14.3	0.40676061	Sensitive
BAD 0.3 uM	Ruxolitinib	tri_12	−0.3860581	Resistant
BAD 0.3 uM	Selinexor	ITIH2	0.33151808	Sensitive
BAD 0.3 uM	Sorafenib	RFX7	0.43405693	Sensitive
BAD 0.3 uM	Sorafenib	i-CLL	−0.449044	Resistant
BAD 0.3 uM	Sorafenib	ZMYM3	0.43405693	Sensitive
BAD 0.3 uM	Sorafenib	GNB1	0.39982624	Sensitive
BAD 0.3 uM	Sunitinib	RFX7	−0.4492304	Resistant
BAD 0.3 uM	Sunitinib	priortrt_Post	−0.3661761	Resistant
BAD 0.3 uM	Sunitinib	U-CLL	−0.3404206	Resistant
BAD 0.3 uM	Sunitinib	FBXW7	−0.3307806	Resistant
BAD 0.3 uM	Sunitinib	KLHL6	0.35719433	Sensitive
BAD 0.3 uM	Sunitinib	loss_11q22.3	−0.3414054	Resistant
BAD 0.3 uM	Sunitinib	loss_2q31.1	−0.3825925	Resistant
BAD 0.3 uM	Sunitinib	ZMYM3	−0.4492304	Resistant
BAD 0.3 uM	Sunitinib	M-CLL	0.34042063	Sensitive
BAD 0.3 uM	Sunitinib	loss_10p12.2	−0.3825925	Resistant
BAD 0.3 uM	Trametinib	CHD2	0.37700492	Sensitive
BAD 0.3 uM	Trametinib	TP53	0.45481052	Sensitive
BAD 0.3 uM	Umbralisib	TP53	0.3904925	Sensitive
BAD 0.3 uM	Umbralisib	NOTCH1	−0.3568164	Resistant
BAD 0.3 uM	Umbralisib	IGLV321_R110	−0.5181869	Resistant
BAD 0.3 uM	Umbralisib	U-CLL	−0.3778123	Resistant
BAD 0.3 uM	Umbralisib	KMT2D	0.40655247	Sensitive
BAD 0.3 uM	Umbralisib	loss_6q	−0.5181869	Resistant

TABLE 2-continued

Gene Drivers and their Sensitivity to CLL Treatment Agents

peptide	drug	feature	dprim_pearson_corr	direction
BAD 0.3 uM	Umbralisib	M-CLL	0.37781234	Sensitive
BAD 0.3 uM	Umbralisib	RPS15	−0.5181869	Resistant
BAD 0.3 uM	Vecabrutinib	NOTCH1	−0.4023258	Resistant
BAD 0.3 uM	Vecabrutinib	IGLV321_R110	−0.3364496	Resistant
BAD 0.3 uM	Vecabrutinib	loss_13q14.3	0.3499221	Sensitive
BAD 0.3 uM	Vecabrutinib	loss_6q	−0.3364496	Resistant
BAD 0.3 uM	Vecabrutinib	RPS15	−0.3364496	Resistant
BAD 0.3 uM	Venetoclax	EC-m3	0.36744156	Sensitive
BAD 0.3 uM	Venetoclax	loss_13q14.3	0.44284898	Sensitive
BAD 0.3 uM	Voruciclib	i-CLL	0.43205742	Sensitive
BAD 0.3 uM	Voruciclib	BIRC3	0.36724922	Sensitive
BAD 0.3 uM	Voruciclib	ITIH2	0.36724922	Sensitive
BAD 0.3 uM	Voruciclib	loss_17q11.2	0.36724922	Sensitive
BAD 0.3 uM	Voruciclib	loss_9p21.3	0.36724922	Sensitive
BAD 0.3 uM	Zanubrutinib	BIRC3	0.38964535	Sensitive
BAD 0.3 uM	Zanubrutinib	priortrt_Post	−0.3621853	Resistant
BAD 0.3 uM	Zanubrutinib	ITIH2	0.38964535	Sensitive
BAD 0.3 uM	Zanubrutinib	tri_12	0.37718588	Sensitive
BAD 0.3 uM	Zanubrutinib	loss_17p13.1	0.38964535	Sensitive
BAD 0.3 uM	Zanubrutinib	loss_17q11.2	0.38964535	Sensitive
BAD 0.3 uM	Zanubrutinib	loss_9p21.3	0.38964535	Sensitive
BIM 0.01 uM	A-1331852	EC-u2	0.36150504	Sensitive
BIM 0.01 uM	A-1331852	CARD11	−0.3550751	Resistant
BIM 0.01 uM	A-1331852	MYD88	−0.347394	Resistant
BIM 0.01 uM	AZD5991	loss_18q21.2	0.34858214	Sensitive
BIM 0.01 uM	AZD5991	loss_15q26.1	0.35512307	Sensitive
BIM 0.01 uM	AZD5991	loss_3p13	0.37182779	Sensitive
BIM 0.01 uM	AZD5991	ANK1	0.35512307	Sensitive
BIM 0.01 uM	AZD5991	loss_1p36.11	0.34858214	Sensitive
BIM 0.01 uM	Abexinostat	loss_17q23.1	0.33522511	Sensitive
BIM 0.01 uM	Abexinostat	priortrt_Post	0.43037204	Sensitive
BIM 0.01 uM	Abexinostat	CNOT3	0.33160882	Sensitive
BIM 0.01 uM	Abexinostat	EC-m2	0.41609565	Sensitive
BIM 0.01 uM	Acalabrutinib	ITIH2	0.38155867	Sensitive
BIM 0.01 uM	Atorvastatin	gain_19p13.3	−0.4238085	Resistant
BIM 0.01 uM	Atorvastatin	RFX7	−0.8943479	Resistant

TABLE 2-continued

Gene Drivers and their Sensitivity to CLL Treatment Agents

peptide	drug	feature	dprim_pearson_corr	direction
BIM 0.01 uM	Atorvastatin	EC-u1	−0.3689004	Resistant
BIM 0.01 uM	Atorvastatin	FBXW7	−0.5147083	Resistant
BIM 0.01 uM	Atorvastatin	loss_10q24.2	−0.3883399	Resistant
BIM 0.01 uM	Atorvastatin	loss_2q31.1	−0.3447146	Resistant
BIM 0.01 uM	Atorvastatin	ZMYM3	−0.8943479	Resistant
BIM 0.01 uM	Atorvastatin	n-CLL	−0.3923104	Resistant
BIM 0.01 uM	Atorvastatin	loss_10p12.2	−0.3447146	Resistant
BIM 0.01 uM	Azacitidine	gain_19p13.3	−0.3533136	Resistant
BIM 0.01 uM	Azacitidine	BIRC3	−0.3752794	Resistant
BIM 0.01 uM	Azacitidine	FBXW7	−0.373508	Resistant
BIM 0.01 uM	Azacitidine	ITIH2	−0.3752794	Resistant
BIM 0.01 uM	Azacitidine	loss_17q11.2	−0.3752794	Resistant
BIM 0.01 uM	Azacitidine	loss_9p21.3	−0.3752794	Resistant
BIM 0.01 uM	Carfilzomib	loss_17q23.1	0.33868438	Sensitive
BIM 0.01 uM	Carfilzomib	EC-m2	0.35202411	Sensitive
BIM 0.01 uM	Cerdulatinib	loss_13q14.3	0.43528141	Sensitive
BIM 0.01 uM	Cerdulatinib	KMT2D	0.33735471	Sensitive
BIM 0.01 uM	Cerdulatinib	loss_13q14.13	0.43008695	Sensitive
BIM 0.01 uM	Crizotinib	EC-i	−0.3441979	Resistant
BIM 0.01 uM	Crizotinib	NOTCHI	−0.451415	Resistant
BIM 0.01 uM	Crizotinib	IGLV321_R110	−0.451415	Resistant
BIM 0.01 uM	Crizotinib	SF3B1	0.34464916	Sensitive
BIM 0.01 uM	Crizotinib	loss_6q	−0.451415	Resistant
BIM 0.01 uM	Crizotinib	RPS15	−0.451415	Resistant
BIM 0.01 uM	Dasatinib	NOTCH1	−0.5258126	Resistant
BIM 0.01 uM	Dasatinib	IGLV321_R110	−0.5258126	Resistant
BIM 0.01 uM	Dasatinib	loss_17q23.1	0.42597941	Sensitive
BIM 0.01 uM	Dasatinib	loss_6q	−0.5258126	Resistant
BIM 0.01 uM	Dasatinib	RPS15	−0.5258126	Resistant
BIM 0.01 uM	Duvelisib	NOTCH1	−0.3445454	Resistant
BIM 0.01 uM	Duvelisib	EC-m2	0.35658655	Sensitive
BIM 0.01 uM	Entospletinib	tri_12	0.43712522	Sensitive
BIM 0.01 uM	Erastin	EC-m1	−0.3427213	Resistant
BIM 0.01 uM	Erastin	ITIH2	−0.3466876	Resistant
BIM 0.01 uM	GSK690693	i-CLL	0.35522406	Sensitive
BIM 0.01 uM	Ibrutinib	CNOT3	−0.4548753	Resistant

TABLE 2-continued

Gene Drivers and their Sensitivity to CLL Treatment Agents

peptide	drug	feature	dprim_pearson_corr	direction
BIM 0.01 uM	Ibrutinib	MYD88	−0.375696	Resistant
BIM 0.01 uM	JQ1	EC-i	0.38264049	Sensitive
BIM 0.01 uM	JQ1	priortrt_Post	0.36086327	Sensitive
BIM 0.01 uM	JQ1	loss_18q21.2	0.43654467	Sensitive
BIM 0.01 uM	JQ1	loss_3p13	0.33635134	Sensitive
BIM 0.01 uM	JQ1	loss_10q24.32	0.43654467	Sensitive
BIM 0.01 uM	JQ1	loss_1p36.11	0.43654467	Sensitive
BIM 0.01 uM	Lenalidomide	loss_15q15.1b	−0.3452293	Resistant
BIM 0.01 uM	Lenalidomide	loss_20p11.22	−0.3452293	Resistant
BIM 0.01 uM	MK-2206	BIRC3	0.35328124	Sensitive
BIM 0.01 uM	MK-2206	ITIH2	0.35328124	Sensitive
BIM 0.01 uM	MK-2206	loss_17q11.2	0.35328124	Sensitive
BIM 0.01 uM	MK-2206	loss_9p21.3	0.35328124	Sensitive
BIM 0.01 uM	Navitoclax	loss_8p	0.39508636	Sensitive
BIM 0.01 uM	Navitoclax	loss_3p21.31	0.41463633	Sensitive
BIM 0.01 uM	Navitoclax	loss_14q32.12	0.38220577	Sensitive
BIM 0.01 uM	Navitoclax	loss_7q36.1	0.39508636	Sensitive
BIM 0.01 uM	Nirogacestat	tri_12	0.33700499	Sensitive
BIM 0.01 uM	Nirogacestat	EC-m2	0.41295567	Sensitive
BIM 0.01 uM	Onalespib	loss_15q15.1b	−0.3983134	Resistant
BIM 0.01 uM	Onalespib	loss_20p11.22	−0.3983134	Resistant
BIM 0.01 uM	Osimertinib	NOTCH1	−0.3688148	Resistant
BIM 0.01 uM	Osimertinib	IGLV321_R110	−0.3688148	Resistant
BIM 0.01 uM	Osimertinib	EC-u2	0.3685819	Sensitive
BIM 0.01 uM	Osimertinib	BIRC3	0.40211777	Sensitive
BIM 0.01 uM	Osimertinib	loss_6q	−0.3688148	Resistant
BIM 0.01 uM	Osimertinib	loss_17q11.2	0.40211777	Sensitive
BIM 0.01 uM	Osimertinib	loss_9p21.3	0.40211777	Sensitive
BIM 0.01 uM	Osimertinib	RPS15	−0.3688148	Resistant
BIM 0.01 uM	Ponatinib	RFX7	−0.4535092	Resistant
BIM 0.01 uM	Ponatinib	EC-i	−0.4254906	Resistant
BIM 0.01 uM	Ponatinib	NOTCH1	−0.4928195	Resistant
BIM 0.01 uM	Ponatinib	IGLV321_R110	−0.4928195	Resistant
BIM 0.01 uM	Ponatinib	i-CLL	−0.3857108	Resistant
BIM 0.01 uM	Ponatinib	priortrt_Post	−0.3481786	Resistant
BIM 0.01 uM	Ponatinib	U-CLL	−0.3892403	Resistant

TABLE 2-continued

Gene Drivers and their Sensitivity to CLL Treatment Agents

peptide	drug	feature	dprim_pearson_corr	direction
BIM 0.01 uM	Ponatinib	loss_2q31.1	−0.3448179	Resistant
BIM 0.01 uM	Ponatinib	ZMYM3	−0.4535092	Resistant
BIM 0.01 uM	Ponatinib	loss_6q	−0.4928195	Resistant
BIM 0.01 uM	Ponatinib	M-CLL	0.38924027	Sensitive
BIM 0.01 uM	Ponatinib	loss_10p12.2	−0.3448179	Resistant
BIM 0.01 uM	Ponatinib	RPS15	−0.4928195	Resistant
BIM 0.01 uM	Ponatinib	m-CLL	0.44631549	Sensitive
BIM 0.01 uM	Rapamycin	RFX7	−0.590868	Resistant
BIM 0.01 uM	Rapamycin	FBXW7	−0.4127982	Resistant
BIM 0.01 uM	Rapamycin	ZMYM3	−0.590868	Resistant
BIM 0.01 uM	Rapamycin	n-CLL	−0.3681718	Resistant
BIM 0.01 uM	Ricolinostat	loss_15q15.1b	−0.3481502	Resistant
BIM 0.01 uM	Ricolinostat	i-CLL	−0.3799749	Resistant
BIM 0.01 uM	Ricolinostat	loss_20p11.22	−0.3481502	Resistant
BIM 0.01 uM	Selinexor	MYD88	0.3956828	Sensitive
BIM 0.01 uM	Sorafenib	gain_19p13.3	−0.340448	Resistant
BIM 0.01 uM	Sorafenib	RFX7	−0.6413425	Resistant
BIM 0.01 uM	Sorafenib	FBXW7	−0.3976621	Resistant
BIM 0.01 uM	Sorafenib	loss_2q31.1	−0.3972096	Resistant
BIM 0.01 uM	Sorafenib	ZMYM3	−0.6413425	Resistant
BIM 0.01 uM	Sorafenib	loss_10p12.2	−0.3972096	Resistant
BIM 0.01 uM	Sorafenib	GNB1	0.39242101	Sensitive
BIM 0.01 uM	Sunitinib	gain_19p13.3	−0.350848	Resistant
BIM 0.01 uM	Sunitinib	RFX7	−0.7282073	Resistant
BIM 0.01 uM	Sunitinib	loss_2q31.1	−0.4921048	Resistant
BIM 0.01 uM	Sunitinib	ZMYM3	−0.7282073	Resistant
BIM 0.01 uM	Sunitinib	n-CLL	−0.3771445	Resistant
BIM 0.01 uM	Sunitinib	loss_10p12.2	−0.4921048	Resistant
BIM 0.01 uM	Trametinib	CHD2	0.56462878	Sensitive
BIM 0.01 uM	Trametinib	loss_14q32.33	−0.3778377	Resistant
BIM 0.01 uM	Umbralisib	NOTCH1	−0.3908108	Resistant
BIM 0.01 uM	Umbralisib	U-CLL	−0.410329	Resistant
BIM 0.01 uM	Umbralisib	EC-m4	0.35101961	Sensitive
BIM 0.01 uM	Umbralisib	M-CLL	0.41032904	Sensitive
BIM 0.01 uM	Venetoclax	SAMHD1	0.33953418	Sensitive
BIM 0.01 uM	Vorinostat	EC-m4	−0.4033298	Resistant

TABLE 2-continued

Gene Drivers and their Sensitivity to CLL Treatment Agents

peptide	drug	feature	dprim_pearson_corr	direction
BIM 0.01 uM	Vorinostat	EC-m2	0.35472621	Sensitive
BIM 0.01 uM	Voruciclib	BCOR	−0.4055636	Resistant
BIM 0.01 uM	Voruciclib	n-CLL	−0.337222	Resistant
BIM 0.01 uM	Zanubrutinib	DICER1	−0.341418	Resistant
BIM 0.01 uM	Zanubrutinib	loss_14q32.33	0.40971541	Sensitive
BIM 0.01 uM	Zanubrutinib	MED1	−0.341418	Resistant
BIM 0.01 uM	Zanubrutinib	EC-m4	−0.3738111	Resistant
BIM 0.01 uM	Zanubrutinib	tri_12	0.44636509	Sensitive
BIM 0.01 uM	Zanubrutinib	EC-m2	0.33298948	Sensitive

[0295] Agents of the present disclosure may be administered within a pharmaceutically-acceptable diluents, carrier, or excipient, in unit dosage form. Conventional pharmaceutical practice may be employed to provide suitable formulations or compositions to administer the compounds to patients suffering from a disease that is caused by excessive cell proliferation (e.g., CLL). Administration may begin before the patient is symptomatic. Any appropriate route of administration may be employed, for example, administration may be parenteral, intravenous, intraarterial, subcutaneous, intratumoral, intramuscular, intracranial, intraorbital, ophthalmic, intraventricular, intrahepatic, intracapsular, intrathecal, intracisternal, intraperitoneal, intranasal, aerosol, suppository, or oral administration. For example, therapeutic formulations may be in the form of liquid solutions or suspensions; for oral administration, formulations may be in the form of tablets or capsules; and for intranasal formulations, in the form of powders, nasal drops, or aerosols.

[0296] Methods well known in the art for making formulations are found, for example, in "Remington: The Science and Practice of Pharmacy" Ed. A. R. Gennaro, Lippincourt Williams & Wilkins, Philadelphia, Pa., 2000. Formulations for parenteral administration may, for example, contain excipients, sterile water, or saline, polyalkylene glycols such as polyethylene glycol, oils of vegetable origin, or hydrogenated napthalenes. Biocompatible, biodegradable lactide polymer, lactide/glycolide copolymer, or polyoxyethylene-polyoxypropylene copolymers may be used to control the release of the compounds. Other potentially useful parenteral delivery systems for agents of the present disclosure include ethylene-vinyl acetate copolymer particles, osmotic pumps, implantable infusion systems, and liposomes. Formulations for inhalation may contain excipients, for example, lactose, or may be aqueous solutions containing, for example, polyoxyethylene-9-lauryl ether, glycocholate and deoxycholate, or may be oily solutions for administration in the form of nasal drops, or as a gel.

[0297] The formulations can be administered to human patients in therapeutically effective amounts (e.g., amounts which prevent, eliminate, or reduce a pathological condition) to provide therapy for a neoplastic disease or condition (e.g., chronic lymphocytic leukemia). The preferred dosage of a nucleobase oligomer of the disclosure is likely to depend on such variables as the type and extent of the disorder, the overall health status of the particular patient, the formulation of the compound excipients, and its route of administration.

[0298] With respect to a subject having chronic lymphocytic leukemia (CLL), an effective amount is sufficient to stabilize, slow, or reduce the proliferation of CLL. Generally, doses of active polynucleotide compositions of the present disclosure would be from about 0.01 mg/kg per day to about 1000 mg/kg per day. It is expected that doses ranging from about 50 to about 2000 mg/kg will be suitable. Lower doses will result from certain forms of administration, such as intravenous administration. In the event that a response in a subject is insufficient at the initial doses applied, higher doses (or effectively higher doses by a different, more localized delivery route) may be employed to the extent that patient tolerance permits. Multiple doses per day are contemplated to achieve appropriate systemic levels of an agent and/or compositions of the present disclosure.

[0299] A variety of administration routes are available. The methods disclosed herein, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode that produces effective levels of the active compounds without causing clinically unacceptable adverse effects. Other modes of administration include oral, rectal, topical, intraocular, buccal, intravaginal, intracisternal, intracerebroventricular, intratracheal, nasal, transdermal, within/on implants, e.g., fibers such as collagen, osmotic pumps, or grafts comprising appropriately transformed cells, etc., or parenteral routes.

Kits

[0300] In another aspect, the disclosure provides kits for aiding in patient selection for treatment and/or characterizing chronic lymphocytic leukemia (e.g., selecting a treatment method for a subject, selection of a subject for a clinical trial, predicting clinical outcome, and the like), which kits are used to detect biomarkers according to the disclosure. In an embodiment, the kit comprises a drug for use in treatment of chronic lymphocytic leukemia (e.g., an agent listed in Table 1A or 2A). In some instances, the kit comprises reagents for collecting a sample from a patient and sequencing RNA from the sample (e.g., RNA-seq). In one embodiment, the kit comprises agents that specifically recognize the biomarkers identified in Tables 3A and 4, or a sub-set thereof. In another embodiment, the kit comprises agents for use in detecting the biomarkers identified in Tables 3A and 4, or a subset thereof. In related embodiments, the agents are antibodies or probes (e.g., oligonucleotides). The kit may contain about or at least about 1, 2, 3, 4, 5, 10, 50, 100, 110, 120, 130, 140, 150, 200 or more different antibodies and/or probes that each specifically recognize one of the biomarkers set forth in Tables 3A and 4.

[0301] In another embodiment, the kit comprises a solid support, such as a chip, a microtiter plate or a bead or resin having capture reagents attached thereon, wherein the capture reagents bind the biomarkers of the disclosure. In the case of biospecfic capture reagents, the kit can comprise a solid support with a reactive surface, and a container comprising the biospecific capture reagents.

[0302] The kit can also comprise a washing solution or instructions for making a washing solution, in which the combination of the capture reagent and the washing solution allows capture of the biomarker or biomarkers on the solid support for subsequent detection by, e.g., mass spectrometry. The kit may include more than one type of adsorbent, each present on a different solid support.

[0303] In a further embodiment, such a kit can comprise instructions for use in any of the methods described herein. In some instances, the kit comprises drug sensitivity information for chronic lymphocytic leukemias (CLLs) having different expression subtypes. The drug sensitivity data is provided in some embodiments along with instructions for selecting a patient for administration of a drug (e.g., an agent listed in Table 1A or 2A) based upon an expression subtype of a chronic lymphocytic leukemia (CLL) in the subject. In embodiments, the instructions provide suitable operational parameters in the form of a label or separate insert. For example, the instructions may inform a consumer about how to collect the sample, how to wash the probe, and/or the particular biomarkers to be detected.

[0304] In yet another embodiment, the kit can comprise one or more containers with controls (e.g., biomarker samples) to be used as standard(s) for calibration.

[0305] The practice of the present disclosure employs, unless otherwise indicated, conventional techniques of molecular biology (including recombinant techniques), microbiology, cell biology, biochemistry and immunology, which are well within the purview of the skilled artisan. Such techniques are explained fully in the literature, such as, "Molecular Cloning: A Laboratory Manual", second edition (Sambrook, 1989); "Oligonucleotide Synthesis" (Gait, 1984); "Animal Cell Culture" (Freshney, 1987); "Methods in Enzymology" "Handbook of Experimental Immunology" (Weir, 1996); "Gene Transfer Vectors for Mammalian Cells" (Miller and Calos, 1987); "Current Protocols in Molecular Biology" (Ausubel, 1987); "PCR: The Polymerase Chain Reaction", (Mullis, 1994); "Current Protocols in Immunology" (Coligan, 1991). These techniques are applicable to the production of the polynucleotides and polypeptides disclosed herein, and, as such, may be considered in making and practicing the disclosure. Particularly useful techniques for particular embodiments will be discussed in the sections that follow.

[0306] The following examples are put forth so as to provide those of ordinary skill in the art with a complete disclosure and description of how to make and use the assay, screening, and therapeutic methods of the disclosure, and are not intended to limit the scope of what the inventors regard as their invention.

EXAMPLES

[0307] By applying Bayesian non-negative matrix factorization for unsupervised clustering of RNA-seq data from 610 treatment-naive CLL samples, 8 robust expression clusters (ECs) were identified. The expression clusters (ECs) strongly associated with IGHV (heavy chain variable region of immunoglobulin genes) mutational status and/or epitype, revealed two subtypes of U-CLL/n-CLL (EC-ul, EC-u2) and four subtypes of M-CLL/m-CLL (EC-m1, EC-m2, EC-m3, and EC-m4) (Tables 3A, 3B, and 4). EC-i was best defined by the i-CLL epitype whereas EC-o, the smallest cluster (n=24; 3.9%), was not significantly associated with any previously defined CLL group. Both EC-i and EC-o displayed borderline identity of somatic hypermutations in IGHV (heavy chain variable region of immunoglobulin genes) with germline, close to the 98% threshold distinguishing M-CLL (CLL with mutated IGHV) from U-CLL (CLL with unmutated IGHV)

[0308] Tables 3, 3B, and 4 relate to the Expression cluster (EC) analysis.

TABLE 3A

Expression cluster (EC) marker genes determined by non-negative matrix factorization

GENE	EC	DIRECTION	RANK	GENE SYNONYM	UNIPROT ID	ENTREZ GENE ID
TFEC	EC-m1	UP	1		O14948	22797
COL18A1	EC-m1	UP	2		P39060	80781
SLC19A1	EC-m1	UP	3		P41440	6573
NRIP1	EC-m1	UP	4		P48552	8204
KCNH2	EC-m1	UP	5		Q12809	3757
SEPT10	EC-u1	UP	1			
LDOC1	EC-u1	UP	2		O95751	23641
LPL	EC-u1	UP	3		P06858	4023
KANK2	EC-u1	UP	4		Q63ZY3	25959
SOWAHC	EC-u1	UP	5		Q53LP3	65124
DUSP26	EC-u1	UP	6		Q9BV47	78986
OSBPL5	EC-u1	UP	7		Q9H0X9	114879
WNT9A	EC-u1	UP	8		O14904	7483
FGFR1	EC-u1	UP	9		P11362	2260
GTSF1L	EC-u1	UP	10		Q9H1H1	149699
EML6	EC-m2	UP	1		Q6ZMW3	400954
HCK	EC-m2	UP	2		P08631	3055
CD1C	EC-m2	UP	3		P29017	911
VPS37B	EC-m2	UP	4		Q9H9H4	79720
CYBB	EC-m2	UP	5		P04839	1536
NXPH4	EC-m2	UP	6		O95158	11247
BTNL9	EC-m2	UP	7		Q6UXG8	153579
KLRK1	EC-m2	UP	8		P26718	100528032
IQSEC1	EC-m2	UP	9		Q6DN90	9922
BANK1	EC-m2	UP	10		Q8NDB2	55024
ACSM3	EC-o	UP	1		Q53FZ2	6296
TOX2	EC-o	UP	2		Q96NM4	84969
PHF16	EC-o	UP	3	JADE3		
SESN3	EC-o	UP	4		P58005	143686
ITGB5	EC-u2	UP	1		P18084	3693
BCL7A	EC-u2	UP	2		Q4VC05	605
PPP1R9A	EC-u2	UP	3		Q9ULJ8	55607
TSPAN13	EC-u2	UP	4		O95857	27075
SLC12A7	EC-u2	UP	5		Q9Y666	10723
SSBP3	EC-u2	UP	6		Q9BWW4	23648
VASH1	EC-u2	UP	7		Q7L8A9	22846
SPG20	EC-u2	UP	8	SPART		
IL13RA1	EC-u2	UP	9		P78552	3597
NR3C2	EC-u2	UP	10		P08235	4306
MS4A4E	EC-m3	UP	1		Q96PG1	643680
MYL9	EC-m3	UP	2		P24844	10398
NT5E	EC-m3	UP	3		P21589	4907
MS4A6A	EC-m3	UP	4		Q9H2W1	64231
PITPNC1	EC-m3	UP	5		Q9UKF7	26207
CNTNAP2	EC-m3	UP	6		Q9UHC6	26047
IGF2BP3	EC-m3	UP	7		O00425	10643
WNT3	EC-m3	UP	8		P56703	101929777
CLDN7	EC-m3	UP	9		O95471	1366
TCF7	EC-m3	UP	10		P36402	6932
MYBL1	EC-m4	UP	1		P10243	4603
NUGGC	EC-m4	UP	2		Q68CJ6	389643
GNG8	EC-m4	UP	3		Q9UK08	94235
GRIK3	EC-i	UP	1		Q13003	2899
IQGAP2	EC-i	UP	2		Q13576	10788
FCER1G	EC-i	UP	3		P30273	2207
STK32B	EC-i	UP	4		Q9NY57	55351
GADD45A	EC-i	UP	5		P24522	1647
P2RX1	EC-m1	DOWN	1		P51575	5023
ARRDC5	EC-m1	DOWN	2		A6NEK1	645432
BEX4	EC-m1	DOWN	3		Q9NWD9	56271
APP	EC-m1	DOWN	4		P05067	351
ADD3	EC-u1	DOWN	1		Q9UEY8	120
AKT3	EC-u1	DOWN	2		Q9Y243	10000
COBLL1	EC-u1	DOWN	3		Q53SF7	22837
MNDA	EC-u1	DOWN	4		P41218	4332
FCRL3	EC-u1	DOWN	5		Q96P31	115352
FAM49A	EC-u1	DOWN	6	CYRIA		
FCRL2	EC-u1	DOWN	7		Q96LA5	79368
SLC2A3	EC-u1	DOWN	8		P11169	6515
MARCKS	EC-u1	DOWN	9		P29966	4082

TABLE 3A-continued

Expression cluster (EC) marker genes determined by non-negative matrix factorization

GENE	EC	DIRECTION	RANK	GENE SYNONYM	UNIPROT ID	ENTREZ GENE ID
LEF1	EC-m2	DOWN	1		Q9UJU2	51176
SH3D21	EC-m2	DOWN	2		A4FU49	79729
FMOD	EC-m2	DOWN	3		Q06828	2331
SEMA4A	EC-m2	DOWN	4		Q9H3S1	64218
CTLA4	EC-m2	DOWN	5		P16410	1493
ADTRP	EC-m2	DOWN	6		Q96IZ2	84830
IGSF3	EC-m2	DOWN	7		O75054	3321
IGFBP4	EC-m2	DOWN	8		P22692	3487
PDGFD	EC-m2	DOWN	9		Q9GZP0	80310
APOD	EC-m2	DOWN	10		P05090	347
TBC1D9	EC-o	DOWN	1		Q6ZT07	23158
PIP5K1B	EC-o	DOWN	2		O14986	8395
SIK1	EC-o	DOWN	3		P57059	150094
DUSP5	EC-o	DOWN	4		Q16690	1847
GNG7	EC-o	DOWN	5		O60262	2788
HIVEP3	EC-o	DOWN	6		Q5T1R4	59269
MARCKSL1	EC-o	DOWN	7		P49006	65108
GPR183	EC-o	DOWN	8		P32249	1880
HRK	EC-o	DOWN	9		O00198	8739
PITPNC1	EC-o	DOWN	10		Q9UKF7	26207
TUBG2	EC-u2	DOWN	1		Q9NRH3	27175
ZNF804A	EC-u2	DOWN	2		Q7Z570	91752
IL2RA	EC-u2	DOWN	3		P01589	3559
BASP1	EC-m3	DOWN	1		P80723	10409
FLJ20373	EC-m3	DOWN	2			
MAP4K4	EC-m3	DOWN	3		O95819	9448
LRRK2	EC-m3	DOWN	4		Q5S007	120892
SAMSN1	EC-m3	DOWN	5		Q9NSI8	388813
CEACAM1	EC-m3	DOWN	6		P13688	634
TNFRSF13B	EC-m3	DOWN	7		O14836	23495
PHF16	EC-m3	DOWN	8	JADE3		
MID1IP1	EC-m3	DOWN	9		Q9NPA3	58526
ABCA9	EC-m3	DOWN	10		Q8IUA7	10350
AEBP1	EC-m4	DOWN	1		Q8IUX7	165
HIP1R	EC-m4	DOWN	2		O75146	9026
LATS2	EC-m4	DOWN	3		Q9NRM7	26524
RIMKLB	EC-m4	DOWN	4		Q9ULI2	57494
EML6	EC-m4	DOWN	5		Q6ZMW3	400954
FADS3	EC-m4	DOWN	6		Q9Y5Q0	3995
MBOAT1	EC-m4	DOWN	7		Q6ZNC8	154141
LCN10	EC-m4	DOWN	8		Q6JVE6	414332
DCLK2	EC-m4	DOWN	9		Q8N568	166614
GLUL	EC-m4	DOWN	10		P15104	2752
ITGAX	EC-i	DOWN	1		P20702	3687
KLF3	EC-i	DOWN	2		P57682	51274
RFTN1	EC-i	DOWN	3		Q14699	23180
PTK2	EC-i	DOWN	4		Q05397	5747
DFNB31	EC-i	DOWN	5			
ZMAT1	EC-i	DOWN	6		Q5H9K5	84460

TABLE 3B

Legend for Table 3A

Column	Description
GENE	Marker gene
EC	Expression cluster
RANK	Rank of marker gene per this EC
GENE SYNONYM	Gene symbol synonym (more updated)
UNIPROT ID	Uniprot protein accession ID
ENTREZ GENE ID	Entrez database gene accession ID

TABLE 4

Biomarkers used in expression cluster (EC) classifier

TRANSCRIPTS PER MILLION (TPM) CLASSIFIER BIOMARKERS	BATCH CORRECTED TRANSCRIPTS PER MILLION (TPM) CLASSIFIER BIOMARKERS
ABCA9	ACAP3
ACAP3	ACSM3
ACSM3	AEBP1
ADAP2	AKT3
AF127936.7	ARHGAP33

TABLE 4-continued

Biomarkers used in expression cluster (EC) classifier

TRANSCRIPTS PER MILLION (TPM) CLASSIFIER BIOMARKERS	BATCH CORRECTED TRANSCRIPTS PER MILLION (TPM) CLASSIFIER BIOMARKERS
ARHGAP33	ARHGAP42
ARMC7	ARMC7
ARRDC5	ARRDC5
ARSD	ATPIF1
ARSI	BACH2
ASB2	BASP1
ATP1A3	BCL7A
ATP2B1	C17orf100
ATPIF1	CBLB
BASP1	CD72
BCL2A1	CD86
BCL7A	CEACAM1
BCS1L	CHPT1
CAMK2A	CLDN7
CLDN23	CMTM7
CMTM7	CNTNAP1
COBLL1	COBLL1
CRELD2	COL18A1
CRY1	CRY1
CTAGE9	CTLA4
CTLA4	EGR3
DDR1	EML6
DKFZP761J1410	EZH2
DPF3	FADS3
EML6	FCER1G
ERRFI1	FCRL2
ESPNL	FGL2
EZH2	FLJ20373
FAHD2B	FMOD
FAM109A	GADD45A
FBXO27	GLIPR1
FGL2	GNB4
FLJ20373	GPR160
FMOD	GPR34
GADD45A	GRIK3
GNAO1	GUCD1
GPR160	HCK
GPR34	HIP1R
GUCD1	HIVEP3
HCK	HMCES
HDAC4	IGF2BP3
HIP1R	IGSF3
HMCES	IL21R
IGSF3	INPP5F
IQSEC1	IQGAP2
ITGAX	IQSEC1
KCNH3	ITGAX
KCNN3	ITGB5
KCTD3	JDP2
KDM1B	KANK2
KLK1	KCNH2
KSR1	KDM1B
LCN10	KLF3
LINC00865	LATS2
LPL	LCN10
LRRK2	LEF1
LUZP1	LPL
MAP4K4	LRRK2
MAPK4	LUZP1
MAST4	MAP4K4
MPRIP	MID1IP1
MRO	MMP14
MSI2	MPRIP
MVB12B	MSI2
MYBL1	MYBL1
MYC	MYL9
MYL5	MYLIP

TABLE 4-continued

Biomarkers used in expression cluster (EC) classifier

TRANSCRIPTS PER MILLION (TPM) CLASSIFIER BIOMARKERS	BATCH CORRECTED TRANSCRIPTS PER MILLION (TPM) CLASSIFIER BIOMARKERS
MYL9	MZB1
MYO3A	NBPF3
NEDD9	NRIP1
NFKBIZ	NRSN2
NR2F6	NUGGC
NRIP1	NXPH4
NRSN2	P2RX1
NUGGC	P2RX5
P2RX1	P2RY14
PELI3	PDGFD
PIGB	PIP5K1B
PIP5K1B	PITPNC1
PITPNC1	PON2
PLD1	PRICKLE1
PTPN7	PTPN7
QDPR	RCN3
REPS2	RDX
RHBDF2	RHBDF2
RIMKLB	RIMKLB
RP11-134N1.2	RNF135
RP11-265P11.1	RP11-145M9.4
RP11-453F18___B.1	RP11-268J15.5
RP11-456H18.2	RP11-463O12.3
RP1-90J20.12	RP5-1028K7.2
SAMSN1	SAMSN1
SCPEP1	SCCPDH
SH3D21	SCD
SLC44A1	SCPEP1
SLC4A7	SDC3
SLC4A8	SECTM1
SMIM10	SESN3
SPN	SH3BP2
SSBP3	SH3D21
STAM	SLC16A5
STX5	SLC19A1
SYNGR3	SLC4A7
TAS1R3	SPN
TBC1D2B	SSBP3
TBC1D9	STX5
TFEC	SUSD1
TIMELESS	TBC1D2B
TNFRSF13B	TBC1D9
TNR	TBKBP1
TOX2	TCF7
TRIM7	TFEC
TUBG2	TGFBR3
VSIG10	TIGIT
WNT5A	TIMELESS
ZMYND8	TMEM133
ZNF804A	TNFRSF13B
	TOX2
	TRAK2
	TTC39C
	TUBG2
	VPS37B
	VSIG10
	WNT9A
	ZAP70
	ZNF667-AS1
	ZNF804A
	ZSWIM6

[0309] The top upregulated marker genes in EC-ul included SEPT10 and LPL. Another upregulated EC-ul gene, OSBPL5, is likely a top expression marker predicting

shorter time to progression after treatment with fludarabine, cyclophosphamide, and rituximab.

[0310] Although EC-o was not associated with IGHV (heavy chain variable region of immunoglobulin genes) status or epitype, it was defined by enrichment in oxidative phosphorylation signaling relative to the other expression clusters (ECs) The EC-m clusters were distinguished by either upregulated or downregulated inflammatory signaling or antigen expression via nonclassical HLA class I. The EC-u clusters shared gene expression changes reflecting impaired protein translation, but were differentiated by TNFα signaling, which was low in EC-ul and high in EC-u2. EC-i was enriched for pathways regulating migration and the humoral immune response, possibly reflecting the autonomous BCR signaling of IGLV3-21^{R110}. Finally, the epiCMIT scores of the expression clusters (ECs) within each epitype were compared. In EC-m clusters, EC-m3 had a lower epiCMIT relative to the other ECs, consistent with a lower proliferative history and suggestive of better patient outcomes. Multivariable analysis that included clinical features and IGHV (heavy chain variable region of immunoglobulin genes) status confirmed independent prognostic impact of the expression clusters (ECs) on failure free survival (FFS) ($n=609$, $p<0.001$) and overall survival (OS) ($p=0.012$) The EC-u clusters had similarly short failure free survival (FFS) and EC-i displayed intermediate failure free survival outcomes in EC-m clusters were distinct where EC-m1, EC-m2, and EC-m4 demonstrated shorter failure free survival (FFS) relative to EC-m3,

Example 1: Drug Treatment Assignment for Chronic Lymphocytic Leukemia (CLL)

[0311] To address the challenge of selecting a proper treatment for a chronic lymphocytic leukemia, experiments were undertaken to optimize high-throughput dynamic BH3 profiling (HT-DBP) for evaluation of the drug sensitivities of CLL samples (FIGS. **1**, **13**, **5**A, **5**B, **6**A, **6**B, and **7**A-**7**C). HT-DBP was optimized as a functional assay that rapidly measured the initiation of apoptotic signaling after ex vivo exposure to drugs for interrogation of CLL samples. Some advantages of the optimized assay were: (i) rapidity—under 24 hours, which is especially important in CLL, where cell viability substantially decreases after 24 hours; (ii) miniaturization—a very limited number of primary cells were required; and (iii) scalability—allowing to conduct hundreds of drug response tests in parallel on one 384-well plate (FIG. **3**). These features collectively maximized the information yield from a given patient sample.

[0312] Prognostic genetic alterations and molecular subtypes of CLL, based on multiomic profiling of>1100 CLL samples have been characterized (Nature Genetics volume 54, pages1664-1674 (2022) the disclosure of which is incorporated herein by reference in its entirety for all purposes). To determine if these molecular findings were associated with novel therapeutic vulnerabilities in CLL, HT-DBP was performed on 65 primary CLL samples previously characterized by exome, transcriptome and methylome profiling (FIGS. **2**A and **2**B), were evaluated using 42 FDA approved drugs that were selected for potential relevance to CLL biology (see Tables 1A and 1B). Peripheral blood mononuclear cells (PBMCs) were isolated and cultured in conditioned media derived from stroma cells to reduce spontaneous apoptosis. Target cells were treated with a drug for 20 hours followed by BH3 peptide exposure. Mitochondrial outer membrane permeabilization (MOMP) was then measured on digitonin-permeabilized cells in response to BH3-only synthetic peptides that mimic pro-apoptotic BCL-2 family proteins. Mitochondrial cytochrome c release was quantified as a measure of MOMP by flow cytometry, gating on CD19+ and CD5+cells. This assay measured if a cell had moved closer to the threshold of apoptosis after drug treatment and thereby identified drugs that enhanced apoptosis priming. The peptides used in each experiment were derived from BIM or PUMA to measure increases in overall apoptotic priming, or BAD and MS1 peptides that identified BCL-2 and MCL-1 dependence, respectively (see FIG. **4**).

[0313] High-throughput dynamic BH3 priming (HT-DBP) results showed high quality and reproducibility (FIGS. **5**A and **5**B). The different BH3 peptides used in HT-DBP showed similar effects.

[0314] The HT-DBP screen revealed differential drug-induced apoptotic priming for various drugs (FIGS. **7**A-**7**C, **8**A, **8**B, **9**, **12**A, **12**B, and **12**C). Venetoclax and ibrutinib, current first-line treatments for CLL, were highly effective across CLL subtypes. Other drugs that demonstrated high priming included navitoclax (BCL-XL/BCL-2), nutlin-3 (MDM2), abexinostat (HDAC), gandotinib (JAK2), duvelisib (PI3Kδ/γ), idelalisib (PI3K6) and cerdulatinib (SYK/JAK). The assay was robust, as indicated by an 0.92 median Pearson correlation across replicates (FIGS. **5**A, **5**B, **6**A, and **6**B). Additionally, the majority of drugs had greater effect on CLL samples than on healthy PBMCs ($p<0.001$, paired t-test), supporting their specificity (FIGS. **7**A-**7**C).

[0315] The analysis of the HT-DBP screen data focused on the differential drug effects among molecular subtypes of CLL (FIGS. **9**, **12**A, **12**B, and **12**C). First, it was found that IGHV-mutated CLLs (M-CLLs) became more primed to apoptosis than IGHV-unmutated CLLs (U-CLLs) across the panel of drugs ($p<0.001$, paired t-test) and that IGHV mutated CLLs had significant response to fludarabine and umbralisib (FDR<0.1, t-test). Second, drug-induced apoptotic priming was compared among 8 CLL subtypes (i.e., RNA expression clusters (ECs); Knisbacher et al. and PCT/US2021/045144, filed Aug. 9, 2021, the disclosures of which are incorporated herein by reference in their entireties for all purposes) (FIGS. **12**A, **12**B, and **12**C). Notable among the many drug priming-EC relationships observed was that within M-CLL ECs, venetoclax was most effective in EC-m3 (high IL-10 expression) and least effective in EC-m2 (low IL-10 and enriched in trisomy 12). Interestingly, EC-m1, which was associated with high TFEC expression and poor outcome, was most sensitive to nutlin-3. For U-CLLs, EC-ul was most sensitive to gandotinib and EC-u2 to navitoclax. EC-i, which was associated with the 20 intermediate methylation subtype of CLL, was the most resistant EC to ibrutinib but was more sensitive to navitoclax than any other drug. Additionally, tri(12) sample groups were observed to be sensitive to treatment via Zanubrutinib and Acalabrutinib, while FBXW7 sample groups exhibited resistance to Zanubrutinib (see FIG. **26**, which provides a table identifying kinase inhibitor drug sensitivities for different peptide concentrations and driver alterations).

[0316] Delta-priming was measured for the molecular features listed along the top of FIGS. **14**, **17**, and **32** using the HT-DBP screen. The molecular features included IGHV subtypes, epitypes, expression subtypes (i.e., expression clusters), mutations in driver genes, and recurrent copy-number events. A feature was included in the heatmap of

FIG. **14** only if at least 2 patients in a DBP screen had the feature. Median delta-priming was computed across all BH3 peptides and across all patients within the feature. FIG. **17** shows median delta priming values for healthy donors per normal cell type, and FIG. **18** shows median delta priming values calculated by subtracting median delta priming values for normal cell types from the delta priming values. Plots showing molecular features for groups of 65 and 81 patients were also compiled (see FIGS. **19**, **20**).

[0317] Additionally, a published dataset of 136 CLL patients with RNA-seq whose samples were screened with 63 drugs was used to compile a plot showing differential drug sensitivity of several expression clusters of interest (see FIG. **23**). Furthermore, a heatmap and dendrogram were compiled in FIGS. **21**A-**21**B, showing significant peptide effect similarity for four peptide groups (PUMA 1 μM, BIM 0.01 μM, BAD 0.3 μM and MSI 2.5 μM).

[0318] A comparison of z-values for dynamic BH3 priming data and cell viability data gathered for chronic lymphocytic leukemia (CLL) cells treated with 13 drugs selected from the 42 listed in Table A2 (see FIGS. **15**, **16**) revealed that the BH3 priming data provided insights into drug efficacy that were not previously available using cell viability data alone. Because the different peptides used could be relatively more promiscuous or more selective for the anti-apoptotic proteins being targeted, use of each of the peptides provided different information with regard to a drug's impact on a CLL cell (see FIG. **29**).

[0319] FIG. **11** showed, together with FIGS. **10**A, **10**B, 1° C., and 1OD that the expression clusters were distinguished by molecular features and drivers.

[0320] Additionally, comparison of CLL sample groups and normal peripheral blood mononuclear cells (PBMCs) revealed that drugs such as Navitoclax and Venetoclax resulted in potentially therapeutically relevant priming in CLL groups, while generating minimal priming response in normal cell groups, indicating that these drugs were efficacious for eliciting an apoptotic response while avoiding potential side effects (see FIGS. **22**A-**22**B). Certain BCL2 inhibitors, such as Venetoclax, can exhibit similar priming responses when combined with peptides that have a BCL2 inhibiting effect, which can help identify new CLL therapies (see FIGS. **28**, **29**). Finally, MCL1 inhibitors were found to exhibit strong effects as part of combination therapies when used together with MS1 peptide, meaning that other MCL1 inhibitors that have a strong priming effect with MS1 peptide would likely be effective as a component in some combination CLL therapies (see FIG. **30**).

[0321] Drug sensitivity results in M-CLL and U-CLL groups were compared by comparing delta-priming or DBP assay output and DKFZ viability assay output at the same concentration, the mean of the two closest (higher and lower) z-scored medians or z-scored means were plotted against each other (see FIGS. **24**A-**24**D). The plots of these results had low correlation, which likely means that the two assays could effectively reveal new information or previously unidentified targets for CLL therapies when used in comparison against each other.

[0322] DBP response with Venetoclax for different driver alterations at different peptide concentrations was also studied, by which the relative drug resistance or sensitivity for Venetoclax therapy was determined for different subtypes (see FIG. **25**). Similarly, the efficacy of Abexinostat was studied by analyzing DBP response under conditions, and was found to be effective in cases where patients would be likely to be resistant to drugs such as Nutlin 3, MK-2206, and Zanubrutinib (see FIG. **27**).

[0323] The level of association for features such as IGHV, epitype, EC subtype, and driver alterations were investigated using delta priming as a representative of drug response across all CLL samples in FIGS. **31**-**38**.

[0324] Median delta-priming for molecular features of interest, including median delta-priming for healthy donors per normal cell type, were shown in FIGS. **39**, **40**, and **41**.

[0325] Altogether, the above examples establish a framework that links ex-vivo drug response with molecular features including expression subtypes to highlight new therapeutic opportunities in CLL. Therefore, drug sensitivity experiment data can be used to inform differential effects among expression clusters (FIG. **13**) and inform treatment selection for a patient with a chronic lymphocytic leukemia.

[0326] The following methods and materials may be employed.

Data Availability Sequencing, expression, and genotyping is available at European Genome-Phenome Archive (EGA), which is hosted at the European Bioinformatics Institute (EBI), under accession numbers EGAS00000000092 and in dbGaP under accession numbers: phs001473, phs000922.v2.pl, phs001431, phs001091.v1.01, phs000435.v3.pl, phs002297.v1, phs000879.v1.pl. 450k array data is available at EGA under accession number EGAD00010001975.

Code Availability

[0327] Terra methods can be found at app.terra.bio/. The new epiCMIT suitable for Illumina arrays and NGS approaches can be found at github.com. The RFcaller pipeline is available at github.com. Additional code used for the project can be found at github.com.

Human Samples

[0328] The 1156 CLL/MBL samples (1010 CLL samples were used in the clinical analysis) included tumor and germline samples collected either during active surveillance (n=687), post-treatment (n=52), or at enrollment of a clinical trial prior to first cycle of therapy (n=417; treatment-naive n=371, relapsed/refractory n=46). Briefly, these trials included: (i) comparison of fludarabine and cyclophosphamide (FC) to FC-rituximab (FCR) in previously untreated patients (CLL8 trial, n=309); (ii) treatment-naive TP53 mutated patients within phase 2 CLL20 trial who all received alemtuzumab (n=31); (iii) ibrutinib or R-ibrutinib in relapsed/refractory (R/R) or untreated patients with 17p deletion, TP53 mutation, and/or 11q deletion (n=77; treatment-naive n=31; R/R n=46). If multiple samples were obtained from a patient, then the earliest collected sample was selected for analysis. Peripheral blood mononuclear cells were isolated and DNA and/or RNA were extracted and prepared as previously described (Stilgenbauer, S. et al. Gene mutations and treatment outcome in chronic lymphocytic leukemia: results from the CLL8 trial. Blood 123, 3247-3254 (2014). Landau, D. A. et al. Mutations driving CLL and their evolution in progression and relapse. Nature 526, 525 (2015); Puente, X. S. et al. Non-coding recurrent mutations in chronic lymphocytic leukaemia. Nature 526, 519 (2015); Gruber, M. et al. Growth dynamics in naturally progressing chronic lymphocytic leukaemia. Nature 570, 474-479 (2019); Landau, D. A. et al. The evolutionary

landscape of chronic lymphocytic leukemia treated with ibrutinib targeted therapy. Nat. Commun. 8, 2185 (2017); Kasar, S. et al. Whole-genome sequencing reveals activation-induced cytidine deaminase signatures during indolent chronic lymphocytic leukaemia evolution. Nat. Commun. 6, 8866 (2015); Burger, J. A. et al. Safety and activity of ibrutinib plus rituximab for patients with high-risk chronic lymphocytic leukaemia: a single-arm, phase 2 study. Lancet Oncol. 15, 1090-1099 (2014); Burger, J. A. et al. Clonal evolution in patients with chronic lymphocytic leukaemia developing resistance to BTK inhibition. Nat. Commun. 7, 11589 (2016)).

Molecular Data Retrieval and Assembly

[0329] Previously reported sequencing data was retrieved from CLL and MBL samples, including 984 whole-exome sequences, 177 whole-genome sequences, 453 RNA-seqs, 490 methylation 450k arrays, and 547 reduced-representation bisulfite sequencing. Additionally, 264 RNA-seq samples were sequenced, and targeted DNA sequencing of the NOTCH]3' UTR was performed for 293 samples, as described below.

RNA-Seq Generation

[0330] For cDNA Library Construction, total RNA was quantified using the Quant-iT RiboGreen RNA Assay Kit and normalized to 5ng/ul. Following plating, 2 μL of ERCC controls (using a 1:1000 dilution) were spiked into each sample. An aliquot of 200ng for each sample underwent library preparation using an automated variant of the Illumina TruSeq Stranded mRNA Sample Preparation Kit, followed by heat fragmentation and cDNA synthesis from the RNA template. The resultant 400 bp cDNA then underwent dual-indexed library preparation, consisting of 'A' base addition, adapter ligation using P7 adapters, and PCR enrichment using P5 adapters. After enrichment, the libraries were quantified using Quant-iT PicoGreen (1:200 dilution). After normalizing samples to 5 ng/uL, the set was pooled and quantified using the KAPA Library Quantification Kit for Illumina Sequencing Platforms.

[0331] For Illumina sequencing, pooled libraries were normalized to 2 nM and denatured using 0.1 N NaOH prior to sequencing. Flowcell cluster amplification and sequencing were performed according to the manufacturer's protocols using the NovaSeq 6000, HiSeq 2000 or HiSeq 2500.

[0332] Each run was a 101 bp paired-end read with eight-base index barcodes. Raw data was analyzed using the Broad Picard Pipeline which includes de-multiplexing and data aggregation.

Sequence Data Processing and Analysis

[0333] All sequencing data (WES, WGS, RNA-seq, RRBS and targeted NOTCH] sequencing) were processed and analyzed using methods implemented in the Broad Institute's cloud-based Terra platform (app.terra.bio).

WES/WGS Alignment and Quality Control

[0334] All DNA sequence data was processed through the Broad Institute's data processing pipeline. For each sample, this pipeline combines data from multiple libraries and flow cell runs into a single BAM file. This file contains reads aligned to the human genome hg19 genome assembly (version b37) done by the Picard and Genome Analysis Toolkit (GATK) developed at the Broad Institute, a process that involves marking duplicate reads, recalibrating base qualities and realigning around indels. Reads were aligned to the hg19 genome assembly (version b37) using BWA-MEM (version 0.7.15-r1140).

Mutation Calling

[0335] Prior to variant calling, the impact of oxidative damage (oxoG) to DNA during sequencing was quantified using DeToxoG (Costello, M. et al. Discovery and characterization of artifactual mutations in deep coverage targeted capture sequencing data due to oxidative DNA damage during sample preparation. Nucleic Acids Res. 41, e67 (2013)). The cross-sample contamination was measured with ContEst based on the allele fraction of homozygous SNPs (Cibulskis, K. et al. ContEst: estimating cross-contamination of human samples in next-generation sequencing data. Bioinformatics 27, 2601-2602 (2011)), and this measurement was used in the downstream mutation calling pipeline. From the aligned BAM files, somatic alterations were identified using a set of tools developed at the Broad Institute (broadinstitute.org/cancer/cga). The details of the sequencing data processing have been described elsewhere (Berger, M. F. et al. The genomic complexity of primary human prostate cancer. Nature 470, 214-220 (2011); Chapman, M. A. et al. Initial genome sequencing and analysis of multiple myeloma. Nature 471, 467-472 (2011)). Briefly, for sSNVs/indel detection, high-confidence somatic mutation calls were made by applying MuTect (Cibulskis, K. et al. Sensitive detection of somatic point mutations in impure and heterogeneous cancer samples. Nat. Biotechnol. 31, 213-219 (2013)), MuTect2 (Benjamin, D. et al. Calling Somatic SNVs and Indels with Mutect2. bioRxiv 861054 (2019) doi:10.1101/861054) and Strelka2 (Kim, S. et al. Strelka2: fast and accurate calling of germline and somatic variants. Nat. Methods 15, 591-594 (2018)) to WES/WGS sequencing data. Given that normal blood samples might also contain CLL cells, DeTiN (Taylor-Weiner, A. et al. DeTiN: overcoming tumor-in-normal contamination. Nat. Methods 15, 531-534 (2018)) was used to estimate tumor in normal (TiN) contamination in order to recover falsely rejected sSNVs/indels. Next, four types of filters were applied: (i) a realignment-based filter, which removes variants that can be attributed entirely to ambiguously mapped reads; (ii) an orientation bias filter, which removes possible oxoG and FFPE artifacts; (iii) a ContEst filter, which removes variants that might come from other samples due to contamination; and (iv) an allele fraction specific panel-of-normals filter, which compares the detected variants to a large panel of normal exomes or genomes and removes variants that were observed in the two panel-of-normals (PoNs): one consists of 8,334 normal samples in TCGA while the other consists of 481 CLL-matched normal samples with TiN estimates of 0. All four filters together contributed to the exclusion of potential false-positive events (e.g. commonly occurring germline variants or sequencing artifacts), which ultimately yielded the final list of mutations. All filtered events in candidate CLL driver genes were also manually reviewed using the Integrated Genomics Viewer (IGV) (Robinson, J. T. et al. Integrative genomics viewer. Nat. Biotechnol. 29, 24-26 (2011)).

[0336] In order to increase the sensitivity and precision of mutation calls in candidate driver genes, an additional variant calling step was performed for the candidate driver

gene loci using Rfcaller (github.com/xa-lab/RFcaller), a pipeline that uses read-level features and extra trees/random forest algorithms for the detection of somatic mutations. This pipeline was run with default parameters for whole exome sequencing (WES) or whole genome sequencing (WGS) data, as well as for RNA-seq data for NOTCH], which has low coverage in hotspot regions in some samples due to high GC content. All candidate mutations that passed filters and were detected by both pipelines were considered positives. Mutations detected by only one of the callers were visually inspected by a set of at least four expert curators, considering the following exclusion criteria: (i) low evidence due to limited number of reads supporting the mutation in the tumor sample or excessive mutant reads in the normal sample; (ii) low depth of coverage to rule out germline variant; (iii) low base quality region; (iv) low mapping quality region leading to multi-mapped reads; (v) calls supported by reads with a strong strand bias.

Identification of Significantly Mutated Genes

[0337] To identify candidate cancer genes using the mutation calls from WES, SignatureAnalyzer (Kim, J. et al. Somatic ERCC2 mutations are associated with a distinct genomic signature in urothelial tumors. Nat. Genet. 48, 600-606 (2016)) was first used to identify mutational processes and potential artifact signatures. A signature likely due to the bleedthrough sequencing artifact was discovered and then mutations with greater than 95% chance attributed to that bleedthrough signature were filtered. Next, MutSig2CV (Lawrence, M. S. et al. Mutational heterogeneity in cancer and the search for new cancer-associated genes. Nature 499, 214-218 (2013)) was run to identify driver genes from the filtered whole exome sequencing (WES) Mutation Annotation Format (MAF) file. A stringent manual review was conducted using the IGV (Robinson, J. T. et al. Integrative genomics viewer. Nat. Biotechnol. 29, 24-26 (2011)) to review the mutations in the driver genes and further exclude low evidence calls. Then MutSig2CV was rerun on the filtered set of mutation calls from whole exome sequencing (WES) to identify the final candidate driver genes. In addition, CLUMPS (Kamburov, A. et al. Comprehensive assessment of cancer missense mutation clustering in protein structures. Proc. Natl. Acad. Sci. U.S.A 112, E5486-95 (2015)) was used to identify driver genes based on clustering of mutations in the 3D structure of the protein product. For CLUMPS, two FDR corrections were applied: one for all candidates and a second restricted hypothesis testing focused on genes in the COSMIC Cancer Gene Census (Sondka, Z. et al. The COSMIC Cancer Gene Census: describing genetic dysfunction across all human cancers. Nat. Rev. Cancer 18, 696-705 (2018)). Finally, for further stringency and to exclude candidates irrelevant to CLL biology, candidate genes that were not expressed in RNA-seq of 610 treatment-naive CLL samples were discarded using a one-sided t-test testing for difference from 0 in transcripts per million (TPM) space. This discarded 15 candidate genes.

UI g.3A>C Mutational Status

[0338] The U1 g.3A>C mutational status for 294 cases from the ICGC cohort was previously reported (Shuai, S. et al. The U1 spliceosomal RNA is recurrently mutated in multiple cancers. Nature 574, 712-716 (2019)). For the remaining 212 ICGC cases, U1 status was determined using a previously validated rhAMP SNP assay (Integrated DNA Technology) (Shuai, S. et al.). The U1 status of 425 patients from the DFCI/Broad cohort was inferred from RNA-seq data using a random forest classifier with 100 trees built from 3,174 differentially spliced introns between U1 mutated and wild-type cases, as previously described (Shuai, et al.). A cohort of 104 cases from the ICGC cohort (7 mutated, 97 wild-type) was used to train the model, while 54 cases (3 mutated, 51 wild-type) were used as a test (Shuai, et al.). Altogether, the U1 g.3A>C status was determined for 931 of 1156 cases.

NOTCH1 Mutation Calling

[0339] A subset of the whole exome sequencing (WES) data had reduced coverage in the GC-rich region of NOTCH], a common and clinically-relevant driver in CLL. The NOTCH] calls from WES/WGS were augmented by Sanger sequencing, targeted deep sequencing of NOTCH]3' UTR (details below), and manual review of all WES, whole genome sequencing (WGS) and RNA-seq in IGV (Robinson, J. T. et al. Integrative genomics viewer. Nat. Biotechnol. 29, 24-26 (2011)). This was primarily focused on identifying NOTCH] hotspot CT deletion p.P2515Rfs*4 and NOTCH]3' UTR mutational hotspot chr9:139390152T>C. RNA-seq review was based on the direct mutation and the splicing perturbation associated with the 3' UTR mutation.

Targeted Sequencing of NOTCH1 3' UTR

[0340] To amplify the region of the NOTCH]3' UTR hotspot mutation at position chr9:139390152T>C and adjacent sequence from genomic DNA, the following PCR1 reaction mix was prepared including 1× PfX amplification buffer, 1× PfX enhancer solution (ThermoFisher, 11708039), 0.3 mM each dNTPs, 1 mM MgSO4, 0.6 μM of NOTCH]1st F-primer, 0.6 μM of Notchl 1stR-primer. To each well of a 96 well plate, 46pL of this mix was added and 2 μL of DNA sample (25ng/pL concentration), and then following PCR reaction was performed: 95° C. 5 min, 33 cycles of (95° C. 30s, 55° C. 30S, 68° C. 1 min), and then held at 4° C. Once the plate was heated to 95° C. for 1 min, the reaction was paused, and the plate was taken out and 2 μL Pfx polymerase mix (1:4 diluted Pfx Polymerase with water) was added into each well, and then the reaction program was continued. In order to add an identifier index onto each amplicon, the PCR2 was performed. First, the following reaction mix was prepared containing 1× Kapa HiFi Fidelity buffer (2 mM $MgCl_2$), 0.41 mM of each dNTPs, 1 μL of Kapa HiFi hotstart polymerase (KapaBiosystems, KK2101), 0.82 μM of the forward primer, and 0.82 μM of each reverse primer (in a 96 well plate). Then 50 μL of the mix was added to anew 96 well plate and 10p L of the PCR1 mix was added to each well of the plate, and the following PCR reaction was performed: 98° C. 45s, 8 cycles of (98° C. 15s, 60° C. 30s, 72° C. 30s), 72° C. 1 min and then held at 4° C. After PCR2, 3 μL of each of the indexed PCR products was pooled and cleaned up using Ampure XP beads. After cleaning, the pooled libraries were quantified using a Bioanalyzer, and then sequenced on a MiSeq using the following parameters: Read 1: 200nt, Read 2: 100nt, Index 1: 8nt, and index 2: 8nt.

Copy Number Analysis

[0341] For detecting somatic copy number alterations (sCNAs) the GATK4 CNV pipeline (github.com/gatk-work-

flows/gatk4-somatic-cnvs) was used, which involves the CalculateTargetCoverage, NormalizeSomaticReadCounts, and Circular Binary Segmentation (CBS) algorithms (Olshen, A. B., Venkatraman, E. S., Lucito, R. & Wigler, M. Circular binary segmentation for the analysis of array-based DNA copy number data. Biostatistics 5, 557-572 (2004)) for genome segmentation. In order to identify candidate somatic copy number alteration (sCNA) drivers (genomic regions that are significantly amplified or deleted), GISTIC 2.0 was then applied (Mermel, C. H. et al. GISTIC2.0 facilitates sensitive and confident localization of the targets of focal somatic copy-number alteration in human cancers. Genome Biol. 12, R41 (2011)). To exclude potential germline CNAs, GISTIC 2.0 was first run on the matched normal samples and then the recurrent CNAs this outputted ($q<0.1$) was concatenated to the blacklisted regions. Then GISTIC 2.0 was run on the tumor samples to produce a list of candidate somatic copy number alteration (sCNA) driver regions. A force-calling process was applied to identify the presence/absence of each somatic copy number alteration (sCNA) driver event across tumor samples (github.com/getzlab/GISTIC2_postprocessing). To further filter the potential false positive drivers, only somatic copy number alteration (sCNA) drivers with population frequency greater than 1% were accepted. Finally, all filtered somatic copy number alteration (sCNA) drivers were manually reviewed using IGV (Robinson, J. T. et al. Integrative genomics viewer. Nat. Biotechnol. 29, 24-26 (2011)) to exclude drivers that are based on somatic copy number alteration (sCNA) events with low supporting evidence or that were localized close to centromeres. Somatic copy number alteration (sCNA) drivers were annotated by intersection with our list of CLL mutation driver genes and with genes in the COSMIC Cancer Gene Census (Sondka, Z. et al. The COSMIC Cancer Gene Census: describing genetic dysfunction across all human cancers. Nat. Rev. Cancer 18, 696-705 (2018)) (v90).

Structural Variants Calling

[0342] For structural variation (SV) detection, the pipeline integrated evidence from three structural variation detection algorithms (Manta (Chen, X. et al. Manta: rapid detection of structural variants and indels for germline and cancer sequencing applications. Bioinformatics 32, 1220-1222 (2016)), SvABA (Wala, J. A. et al. SvABA: genome-wide detection of structural variants and indels by local assembly. Genome Res. 28, 581-591 (2018)) and dRanger (Berger, M. F. et al. The genomic complexity of primary human prostate cancer. Nature 470, 214-220 (2011); Bass, A. J. et al. Genomic sequencing of colorectal adenocarcinomas identifies a recurrent VTITA-TCF7L2 fusion. Nat. Genet. 43, 964-968 (2011); Chapman, M. A. et al. Initial genome sequencing and analysis of multiple myeloma. Nature 471, 467-472 (2011)) to generate a list of structural variation events with high confidence. The three SV detection tools were followed with BreakPointer (Drier, Y. et al. Somatic rearrangements across cancer reveal classes of samples with distinct patterns of DNA breakage and rearrangement-induced hypermutability. Genome Res. 23, 228-235 (2013)) to pinpoint the exact breakpoint at base-level resolution. Breakpoint information was aggregated per sample to identify: (i) balanced translocations, which were defined as those with breakpoints on reverse strands within 1-kb of each other; (ii) inversions supported on both ends; (iii) complex events, based on the number of clustered events within 50-kb of each other. Breakpoints were annotated by intersection with the lists of CLL driver genes and significant somatic copy number alteration (sCNA) regions, as well as with 20 genes in the COSMIC Cancer Gene Census (v90) (Sondka, Z. et al. The COSMIC Cancer Gene Census: describing genetic dysfunction across all human cancers. Nat. Rev. Cancer 18, 696-705 (2018)).

Identification of Structural Variants Involving the Immunoglobulin (IG) Loci

[0343] Potentially oncogenic structural variants involving any of the IG loci were analyzed using IgCaller (v1.1) (Nadeu, F. et al. IgCaller for reconstructing immunoglobulin gene rearrangements and oncogenic translocations from whole-genome sequencing in lymphoid neoplasms. Nat. Commun. 11, 3390 (2020)) and visually inspected in IGV (Robinson, J. T. et al. Integrative genomics viewer. Nat. Biotechnol. 29, 24-26 (2011)). The breakpoints of the IG loci were used to determine the underlying mechanisms leading to these events. To that end, a search was done for evidence of aberrant V(D)J recombination (i.e., breakpoints in any of the V(D)J genes and close to recombination-activation gene (RAG) signal sequences) or aberrant class switch recombination (CSR) (i.e., breakpoints located in any of the CSR regions). IG genes and CSR regions were annotated based on the annotations used by IgCaller. Of note, no evidence of IG structural variants mediated by somatic hypermutation (SHM) were identified (i.e., events with breakpoints within already rearranged V(D)J genes linked with the presence of SHM).

Estimation of Purity, Ploidy, and Cancer Cellfraction (CCF)

[0344] To estimate sample purity, ploidy, absolute allele-specific copy number and cancer cell fraction (CCF) of the filtered whole exome sequencing (WES) somatic coding mutations, ABSOLUTE (Carter, S. L. et al. Absolute quantification of somatic DNA alterations in human cancer. Nat. Biotechnol. 30, 413-421 (2012)) was used, which integrates allele fraction specific information from the sequencing data for sSNVs/indels and sCNAs. For each sample, manual review was conducted to determine the optimal ABSOLUTE solution. Using these ABSOLUTE solutions allowed for recovery of CCF estimates for 49,882 coding mutations of all 53,489 mutations (93.3%) identified in whole exome sequencing (WES) data.

[0345] Timing Analysis

[0346] To infer phylogenetic and evolutionary trajectories based on somatic mutations and copy number variation, PhylogicNDT Cluster, Timing, LeagueModel modules were applied (Leshchiner, I. et al. Comprehensive analysis of tumour initiation, spatial and temporal progression under multiple lines of treatment. bioRxiv 508127 (2019)) (github: github.com/broadinstitute/PhylogicNDT) on the filtered whole exome sequencing (WES) MAF with CCF annotated from the optimal ABSOLUTE solution. To determine if shared events had significantly different order of acquisition in M-CLL (CLL with mutated IGHV) and U-CLL, the timing score was randomly sampled 250,000 times for each shared event from the MCMC traces of M-CLL (CLL with mutated IGHV) and U-CLL (CLL with unmutated IGHV) respectively, and the difference between the two scores was calculated. Then the frequency of the differences being less than 0 was calculated. If the frequency was less than 0.5,

then the p-value was assigned as two times the frequency to that event, i.e. p-value=2*freq; else, the p-value was assigned as two times one minus the frequency to that event, i.e. p-value=2*(1-freq). Then the Benjamini-Hochberg multiple hypothesis correction procedure was applied to all the p-values of shared driver events. The timing of a shared driver event was considered significantly different between the two subtypes if the corresponding q value was less than 0.1.

Gene Set Enrichment for Driver Genes

[0347] Gene set enrichment analysis was performed using g:profilerhttps://paperpile.com/c/CLn83y/PrfG (Reimand, J. et al. g:Profiler-a web server for functional interpretation of gene lists (2016 update). Nucleic Acids Res. 44, W83-9 (2016)) on the 97 driver genes, the total identified in the MutSig and CLUMPS analyses for "All," M-CLL, and U-CLL (CLL with unmutated IGHV) (excluding genes detected only by CLUMPS restricted hypothesis testing for cancer genes, n=2; and excluding 5 genes not found in the gene set annotation). Gene sets from MSigDB v7.0 were used, aggregating Hallmark, C5:GO:BP and C2:CP:REACTOME collections. g:profiler results were filtered by q<0.1, restricted in size between 5 and 350 genes in the gene set, and required to include at least two drivers. To identify similar biological processes and remove redundancy in overlapping gene sets, significant gene sets were clustered using Louvain clustering (Blondel, V. D., Guillaume, J.-L., Lambiotte, R. & Lefebvre, E. Fast unfolding of communities in large networks. arXiv [physics.soc-ph](2008)) (igraph R package v1.2.5). To that end, a gene set network was constructed, where nodes were gene sets and edges are weighted based on shared gene membership by Jaccard index. Three cutoffs for the Jaccard index (0.9, 0.95, 0.99) were applied before clustering to produce different clustering resolutions. The clustering was repeated twice, considering membership by shared drivers or any shared genes between the gene sets. Results were reviewed and biological processes were generalized manually. Candidate genes that were not enriched in gene sets by this process were assigned to pathways by data curation.

Immunoglobulin (IG) Gene Characterization

[0348] The IG heavy (IGH) and light (IGL) chain gene rearrangements and mutational status were obtained from WGS/WES and RNA-seq using IgCaller (v1.1) (Nadeu, F. et al. IgCaller for reconstructing immunoglobulin gene rearrangements and oncogenic translocations from whole-genome sequencing in lymphoid neoplasms. Nat. Commun. 11, 3390 (2020)) and MiXCR (v.3.0.10) (Bolotin, D. A. et al. MiXCR: software for comprehensive adaptive immunity profiling. Nat. Methods 12, 380-381 (2015)), respectively. The rearrangements obtained were visually inspected in IGV (Robinson, J. T. et al. Integrative genomics viewer. Nat. Biotechnol. 29, 24-26 (2011)). IGH gene rearrangements were complemented with Sanger sequencing available for 1085 cases. The IGHV (heavy chain variable region of immunoglobulin genes) mutational status obtained by IgCaller (WGS/WES) and MiXCR were concordant in 506/516 (98%) cases with an IGH rearrangement identified by both methods. The 10 discordant cases were classified based on the IGHV (heavy chain variable region of immunoglobulin genes) mutational status determined by Sanger sequencing (concordant with MiXCR in 8 cases and with IgCaller in 2). IgCaller/MiXCR and Sanger sequencing were concordant in 903/925 (98%) of the cases with an IGH gene rearrangement obtained by both methodologies. The result obtained by IgCaller/MiXCR was used in the 22 discordant cases after careful examination of the sequences. Note that in 12/22 cases the results obtained by IgCaller and MiXCR were concordant. For the remaining 10 cases, only IgCaller or MiXCR results were available. The IGHV (heavy chain variable region of immunoglobulin genes) mutational status of 14 cases carrying a mix of mutated and unmutated IGH gene rearrangements was considered as "not available". Similarly, the IGH genes in 43 cases carrying two IGH rearrangements (the previous 14 cases with mixed IGHV (heavy chain variable region of immunoglobulin genes) mutational status and 29 cases with two mutated or two unmutated IGH gene rearrangements) were considered as "not available". Altogether, 1136/1154 (98%) cases were classified based on their IGHV (heavy chain variable region of immunoglobulin genes) mutational status. To study B-cell receptor (BCR) stereotypy, the 19 major stereotype subsets were annotated using the ARResT/AssignSubsets online tool (Bystry, V. et al. ARResT/AssignSubsets: a novel application for robust subclassification of chronic lymphocytic leukemia based on B cell receptor IG stereotypy. Bioinformatics 31, 3844-3846 (2015)).

[0349] IGL gene rearrangements obtained by IgCaller and MiXCR were concordant in all but five cases with both methods available (581/586, 99%). The output of MiXCR was accepted in the five discordant cases after manual revision. As performed for IGH gene rearrangements, cases carrying two IG populations with distinct IG gene rearrangements were blacklisted from the IGL gene annotation. To properly characterize the IGLV3-21R^{110}, IGLV3-21 rearranged sequences reported by IgCaller were manually curated to phase single nucleotide polymorphisms with the rearranged allele, as previously described (Nadeu, F. et al. IGLV3-21R110 identifies an aggressive biological subtype of chronic lymphocytic leukemia with intermediate epigenetics. Blood (2020) doi: 10.1182/blood.2020008311). Curated IGLV3-21-rearranged sequences from IgCaller and original IGLV3-21-rearranged sequences from MiXCR (in which the manual phasing of polymorphisms is not needed) were used as input of IMGT/V-QUEST (v3.5.18; release 202018-4) (Brochet, X., Lefranc, M.-P. & Giudicelli, V. IMGT/V-QUEST: the highly customized and integrated system for IG and TR standardized V-J and V-D-J sequence analysis. Nucleic Acids Res. 36, W503-8 (2008)) to annotate the IGLV3-21 allele, the motifs involved in BCR-BCR interactions [lysine (K) 16 and aspartates (D) 50 and 52], and the presence of the glycine to arginine mutation at position 110 (R110) (Nadeu, F. et al. IGLV3-21R110 identifies an aggressive biological subtype of chronic lymphocytic leukemia with intermediate epigenetics. Blood (2020) doi:10.1182/blood.2020008311). Overall, IGLV3-21^{R}110 status was determined in 1128/1154 (97.7%) cases.

RNA-Seq Analysis

[0350] RNA-seq data was processed in Terra using the GTEx V7 pipeline (github.com/broadinstitute/gtex-pipeline). Briefly, reads were aligned with STAR (v2.6.1d) (Dobin, A. et al. STAR: ultrafast universal RNA-seq aligner. Bioinformatics 29, 15-21 (2013)) to hg19 (b37) using the GENCODE v19 annotation, and quality control metrics and

gene expression were computed with RNA-SeQC (v2.3.6) (Graubert, A., Aguet, F., Ravi, A., Ardlie, K. G. & Getz, G. RNA-SeQC 2: Efficient RNA-seq quality control and quantification for large cohorts. Bioinformatics (2021) doi:10.1093/bioinformatics/btabl35). A collapsed version of the GENCODE annotation was used to quantify gene-level expression (available from gs://gtex-resources/GENCODE/gencode.v19.genes.v7.collapsed_only.patched_contigs.gtf). Transcripts per million (TPMs) were used for sample clustering, while gene counts were used for differential gene expression, as required.

RNA Expression Cluster Detection

[0351] Gene-level transcripts per million (TPMs) were estimated with RNA-SeQC (v2.3.6) for RNA-seq from 610 treatment-naive CLL. Genes expressed at less than 0.1 transcripts per million (TPM) in 10% of samples were discarded, retaining 11,119 genes, which were batch corrected (as described below), followed by selection of the top 2,500 most varying genes. The clustering methodology combined consensus hierarchical clustering and Bayesian non-negative matrix factorization (BayesNMF), as previously described (Robertson, A. G. et al. Comprehensive Molecular Characterization of Muscle-Invasive Bladder Cancer. Cell 171, 540-556.e25 (2017)). Briefly, the method computed a distance matrix 1-C, where element C_{ij} represented the Spearman correlation between samples i and j across the 2,500 genes. It used the distance matrix to perform iterations of standard hierarchical clustering with 80% sample resampling for 250 iterations per value of parameter K, where K represents the cutoff for the number of clusters running from 2 to 20. The result was the cumulative consensus matrix M, where M_{ij} represents the number of times samples i and j shared cluster membership, which was then normalized by the total number of iterations to create the matrix M*. Next, BayesNMF was performed on M* to identify the optimal number of clusters K* and computed the strength of association of each sample to each cluster. The maximum association determined final cluster assignment. By parallelization, the number of independent BayesNMF runs was increased from 20 to 1000, 77.4% of which converged to the dominant result of K*=8 clusters (20% K*=7, 1.8% K*=6).

RNA-Seq Batch Effect Correction

[0352] Preprocessing of RNA-seq data for expression cluster detection was undertaken to address batch effects between samples collected at different centers and processed by different protocols. To that end, a comprehensive set of covariates was assembled that allowed for adequate control for technical artifacts: (i) Quality metrics from RNA-SeQC v2.3.6 (Graubert, A., Aguet, F., Ravi, A., Ardlie, K. G. & Getz, G. RNA-SeQC 2: Efficient RNA-seq quality control and quantification for large cohorts. Bioinformatics (2021) doi:10.1093/bioinformatics/btabl35); (ii) CIBERSORT (Chen, B., Khodadoust, M. S., Liu, C. L., Newman, A. M. & Alizadeh, A. A. Profiling Tumor Infiltrating Immune Cells with CIBERSORT. Methods Mol. Biol. 1711, 243-259 (2018)) relative immune cell composition estimates (cibersort.stanford.edu/) where B-cell estimates were excluded to prevent masking CLL-intrinsic signals; (iii) PEER factors (Stegle, O., Parts, L., Durbin, R. & Winn, J. A Bayesian framework to account for complex non-genetic factors in gene expression levels greatly increases power in eQTL studies. PLoS Comput. Biol. 6, e1000770 (2010)); (iv) Sex, which was systematically inferred by KMeans clustering (sklearn v0.21.3) using XIST and RPS4Y1 gene expression; (v) explicit sequencing batch if available; (vi) sequencing center (Broad Institute or Barcelona); (vii) a metric devised to estimate the sample processing artifact described in Dvinge et al (Dvinge, H. et al. Sample processing obscures cancer-specific alterations in leukemic transcriptomes. Proceedings of the National Academy of Sciences 111, 16802-16807 (2014)). This metric was computed by Spearman correlation between a sample's expression profile to the genes reported by Dvinge et al to be differentially expressed after 48 hours of incubation at suboptimal temperatures. However, to reduce the potential contribution of CLL-related expression to this metric, the correlation was computed by focusing on 3,682 differentially expressed genes that have been previously defined as house-keeping genes (Eisenberg, E. & Levanon, E. Y. Human housekeeping genes, revisited. Trends Genet. 29, 569-574 (2013)). Of note, covariates from RNA-SeQC (Graubert, A., Aguet, F., Ravi, A., Ardlie, K. G. & Getz, G. RNA-SeQC 2: Efficient RNA-seq quality control and quantification for large cohorts. Bioinformatics (2021) doi:10.1093/bioinformatics/btabl35) and CIBERSORT were converted to PCA space. Top PCs and PEER factors were selected as appropriate. Batch correction for expression cluster (EC) detection was performed by including the covariates as fixed effects in a linear model to regress out effects they were associated with, and sample clustering was performed on the resulting residuals.

Marker Gene Detection and Differential Expression Analysis

[0353] To identify marker genes per expression cluster, a second non-negative matrix factorization step was applied, as previously described (Robertson, A. G. et al. Comprehensive Molecular Characterization of Muscle-Invasive Bladder Cancer. Cell 171, 540-556.e25 (2017)). However, in this study, batch-corrected transcripts per million (TPMs) were used and a fold-change of 1.5 was required between each cluster and all others. Markers selected were limited to the top 10 most up and down regulated genes per expression cluster (EC) (Tables 3A-3B and 4). Additionally, limma-voom (Ritchie, M. E. et al. limma powers differential expression analyses for RNA-sequencing and microarray studies. Nucleic Acids Res. 43, e47 (2015); Law, C. W., Chen, Y., Shi, W. & Smyth, G. K. voom: Precision weights unlock linear model analysis tools for RNA-seq read counts. Genome Biol. 15, R29 (2014)) was used to identify differentially expressed genes between each expression cluster (EC) and all others. The same covariates used for RNA-seq batch effect correction for expression cluster discovery were included in the models, while using unmodified gene counts from RNA-SeQC (Graubert, A., Aguet, F., Ravi, A., Ardlie, K. G. & Getz, G. RNA-SeQC 2: Efficient RNA-seq quality control and quantification for large cohorts. Bioinformatics (2021) doi:10.1093/bioinformatics/btabl35). Genes with $q<0.05$ and absolute fold-change greater than 1.5 were considered differentially expressed (Tables 3A-3B and 4).

Gene Set Enrichment Analysis for Expression Clusters (ECs)

[0354] Gene set enrichment per each expression cluster was performed using fgsea (github.com/ctlab/fgsea) (Koro-

tkevich, G. et al. Fast gene set enrichment analysis. bioRxiv 060012 (2021) doi:10.1101/060012), which was applied to the W matrix produced by the second BayesNMF step that detected marker genes associated with each expression cluster (EC) (see Robertson et al. (Robertson, A. G. et al. Comprehensive Molecular Characterization of Muscle-Invasive Bladder Cancer. Cell 171, 540-556.e25 (2017)) for details). In essence, this represents gene lists ranked by their association with each EC, ranging from most positively associated to most negatively associated. Gene sets from MSigDB v7.0 were used, aggregating Hallmark, C5:GO:BP and C2:CP:REACTOME collections. Analysis was restricted to gene sets of size 12 to 500, and q<0.1 was required. For further confidence, we applied Gene Set Variation Analysis (GSVA) from the gsva R package (Hanzelmann, S., Castelo, R. & Guinney, J. GSVA: gene set variation analysis for microarray and RNA-seq data. BMC Bioinformatics 14, 7 (2013)) using the top 2500 most varying genes. GSVA estimates were summarized per expression cluster (EC) and mean differences computed between each expression cluster (EC) and all others. The intersection of results from fgsea and GSVA was retained.

[0355] Next, to identify related biological processes and remove redundancy in overlapping gene sets, significant gene sets were clustered using Louvain clustering (Blondel, V. D., Guillaume, J.-L., Lambiotte, R. & Lefebvre, E. Fast unfolding of communities in large networks. arXiv [physics. soc-ph](2008)) (igraph R package v1.2.5). To that end, a gene set network was constructed, where nodes were gene sets and edges were weighted based on shared gene membership by Jaccard index (using genes in the "leading edge" reported by fgsea). Three cutoffs for Jaccard index (0.8, 0.9, 0.95) were applied before clustering to produce different clustering resolutions. Finally, results were reviewed and biological processes were generalized manually. Only gene sets with absolute NES scores>2 fromfgsea and a>0.1 difference in mean GSVA score between the respective expression cluster (EC) and all other samples were considered.

Detection of Statistically Significant Pairwise Associations of Molecular Features

[0356] To identify statistically significant pairwise associations of molecular features (e.g., association of expression clusters (ECs) with candidate drivers), the curveball permutation algorithm (Strona, G., Nappo, D., Boccacci, F., Fattorini, S. & San-Miguel-Ayanz, J. A fast and unbiased procedure to randomize ecological binary matrices with fixed row and column totals. Nat. Commun. 5, 4114 (2014)) was applied to a comprehensive sample annotation table to generate the null distribution of the p-value from one-sided Fisher's Exact tests for each pair of features. The sample annotation table contained binary indicators for all sSNV/indel drivers and somatic copy number alteration (sCNA) drivers identified, in addition to U1 mutation, IGLV3-21^{R110} mutation, IGHV (heavy chain variable region of immunoglobulin genes) mutational status, expression clusters (ECs) and epitypes. Samples that had DNA, RNA and methylation data were focused upon, and they were also required to be treatment-naive (n=506). The goal of the curveball algorithm was to estimate an accurate null distribution through controlling the sample-level driver mutation rates, which reduced false positive associations caused by background mutation burdens. 5000 curveball permutation iterations were applied to generate this null distribution and then the observed p-value was compared against it to get the empirical p-value for co-occurring and mutual-exclusive patterns for each feature pair. The Benjamini-Hochberg procedure was then applied to the empirical p-values and the significant events were selected (q<0.1) (Benjamini, Y. & Hochberg, Y. Controlling the false discovery rate: A practical and powerful approach to multiple testing. J. R. Stat. Soc. 57, 289-300 (1995)).

Expression Cluster Machine-Learning Classifier

[0357] The 610 treatment-naive RNA-seqs of the expression cluster (EC) discovery set were split into a training set (n=487, 80%) and test set (n=123, 20%). The latter was used to assess performance after final model selection. Features used in the model were derived from differential expression results between expression clusters (ECs) using limma-voom (Ritchie, M. E. et al. limma powers differential expression analyses for RNA-sequencing and microarray studies. Nucleic Acids Res. 43, e47 (2015)) on training set samples. Models were trained using the RandomForestClassifier class in the sklearn (v0.22.2) Python package (with parameter class weight="balance subsample" to mitigate class imbalance in the models). Hyperparameters were optimized using 5-fold cross validation and model performance was evaluated by the harmonic mean of overall accuracy and macroFI (mean F1 across ECs). The final performance metric per hyper-parameter set was the mean of this value across cross-validation folds. Hyperparameters screened included forest size (500, 1000), number of most differentially expressed genes used from each comparison in limma-voom (5, 10, 20, 50) and oversampling method from the imblearn package (v0.6.2) used to improve performance (ADASYN, BorderlineSMOTE, SMOTE, SVMSMOTE or None). DESeq-normalized transcripts Per Million (TPMs) were used primarily and the process was repeated for batch-corrected transcripts Per Million (TPMs) to assess the impact of batch-correction on performance. Reported accuracy metrics were computed by applying the selected models to the test set.

Stability Assessment of Expression Clusters

[0358] CLL RNA-seq data generated across multiple timepoints was analyzed prior to treatment from 19 patients (Gruber, M. et al. Growth dynamics in naturally progressing chronic lymphocytic leukaemia. Nature 570, 474-479 (2019)), focusing on two time points per patient in 18 of 19 cases. For one patient, CRC-0019, all 6 samples available were analyzed prior to treatment. The machine learning expression cluster (EC) classifier was applied to these 42 samples to obtain predicted expression cluster (EC) assignments. Importantly, to avoid biases for these patient samples, the classifier was retrained while excluding these patients from the training process. Then, to test if the assignment of expression clusters (ECs) was consistent over time more than expected by chance, a permutation test was performed, randomizing all labels among the 42 samples 1,000,000 times. For each permutation a value H_{perm} was computed by the sum of Shannon's entropy per patient. For example, a patient with consistent assignment in 2 samples contributed 0 bits to H_{perm}, whereas a patient with two different labels contributed 1 bit. The mean H_{perm} value was 10.47, compared to H_{real} from the actual data that was 2.77. No

randomizations were as low as this, providing a p-value<10^{-6} in support of expression cluster (EC) stability. This was based on stability in 15 of 19 patients, where 2/15 were classified differently than in the expression cluster (EC) discovery process. Considering 13/19 (68.4%), expression clusters (ECs) were consistent over time in most patients.

DNA Methylation Data Processing

[0359] DNA methylome data was analyzed for a total of 1,037 samples, including 490 samples profiled with Illumina 450k array previously analyzed (Duran-Ferrer, M. et al. The proliferative history shapes the DNA methylome of B-cell tumors and predicts clinical outcome. Nature Cancer 1, 1066-1081 (2020)) (EGA accession EGAD00010001975), and 547 samples profiled using reduced representation bisulfite sequencing (RRBS, with either single-end (SE), or paired-end (PE) approaches) (Landau, D. A. et al. Locally disordered methylation forms the basis of intratumor methylome variation in chronic lymphocytic leukemia. Cancer Cell 26, 813-825 (2014)). A pipeline in Terra was developed to obtain the CpG methylation estimates from RRBS data. First, FASTQC (bioinformatics.babraham.ac.uk/projects/fastqc/) and MultiQC (Ewels, P., Magnusson, M., Lundin, S. & Kdller, M. MultiQC: summarize analysis results for multiple tools and samples in a single report. Bioinformatics 32, 3047-3048 (2016)) were used for quality control. Trimming was applied to the PE samples as appropriate for the RRBS protocol. Next, reads were aligned to hgl9 using BSMAP (Xi, Y. & Li, W. BSMAP: whole genome bisulfite sequence MAPping program. BMC Bioinformatics 10, 232 (2009)) (v2.90) and methylation was called with the mcall module from the MOABS package (Sun, D. et al. MOABS: model based analysis of bisulfite sequencing data. Genome Biol. 15, R38 (2014)) (v1.3.9.6). For SE samples, BSMAP was run with flags "-v 0.1-s 12-q20-w100-S1-u-R-DC-CGG-r 0", and for PE samples with "-v0.1-s12-q20-w100-S1-u-R-r0". mcall was run with flag "-F 256", for primary alignments only. For downstream analysis, only CpGs covered by at least 5 reads were retained. 14 samples were then removed from the initial 1,037, since they did not pass the filtering criteria due to poor bisulfite conversion rates, poor alignment metrics, suspected contaminations from other samples, extremely low number of methylated CpGs, and/or very low number of CpGs with 5 reads compared to the general distribution. After all filtering criteria, a total of 1,023 samples were used for all downstream analyses. From these 1,023 samples, 24 were profiled twice with different platforms and were used to validate the robustness of the new epiCMIT (Duran-Ferrer, M. et al. The proliferative history shapes the DNA methylome of B-cell tumors and predicts clinical outcome. Nature Cancer 1, 1066-1081 (2020)) epigenetic mitotic clock across platforms (18 profiled with Illumina 450k vs RRBS-PE, and 6 profiled with RRBS-PE vs RRBS-SE). In these 24 cases, the platform with more CpGs covered across all samples was prioritized (from the highest to lowest priority, Illumina 450k>RRBS-PE>RRBS-SE). The remaining 999 unique samples included 490 profiled by Illumina 450k array, 390 by RRBS-SE and 119 by RRBS-PE (3 samples were not included in consensus matrices due to lower number of CpGs, including 2 RRBS-SE and 1 RRBS-PE samples). The consensus matrices for each platform with shared CpGs across samples contained 447,800 CpGs and 490 samples for Illumina 450k data; 44,363 CpGs and 388 samples for RRBS-SE data; and 173,808 CpGs and 136 samples for RRBS-PE data [18 of these 136 samples were only used to test epiCMIT robustness across platforms, as they were already profiled with Illumina 450k; 6 of the remaining 118 RRBS-PE samples were also profiled with RRBS-SE to test epiCMIT robustness across platforms (analyzed separately and not included in the RRBS-SE consensus matrix), but were subsequently discarded and only their corresponding RRBS-PE samples were retained according to the aforementioned platform prioritization scheme]. These consensus matrices were used to perform principal component analyses (PCA) and in the case of RRBS data, also to assign CLL epitypes.

CLL Epitype Classification

[0360] The CLL epitypes were calculated for all 1,023 450k/RRBS samples. In the case of Illumina 450k data, a recently published algorithm was used which uses 4 CpGs and is suitable for both Illumina 450k and EPIC arrays (Duran-Ferrer, M. et al. The proliferative history shapes the DNA methylome of B-cell tumors and predicts clinical outcome. Nature Cancer 1, 1066-1081 (2020)). For RRBS data, the previously created consensus matrices created for RRBS-SE and RRBS-PE platforms were used separately and the following strategy was used: CLL patients with 100% and <95% IGHV (heavy chain variable region of immunoglobulin genes) identities were selected to perform differential DNA methylation analysis with mean methylation fraction differences between groups of at least 0.5. These IGHV (heavy chain variable region of immunoglobulin genes) cutoffs yielded 168 and 80 samples for RRBS-SE data, and 67 and 13 samples for RRBS-PE data with IGHV (heavy chain variable region of immunoglobulin genes) identities of 100% and <95%, respectively. These stringent cutoffs were imposed for both IGHV (heavy chain variable region of immunoglobulin genes) and DNA methylation differences to avoid borderline cases, compared with the traditional 98% IGHV (heavy chain variable region of immunoglobulin genes) and 0.25 methylation difference cutoffs. This filtering criteria translated into clearer signatures consisting of 32 and 153 differentially methylated CpGs for RRBS-SE and RRBS-PE data, respectively. These CpGs were then used to perform consensus clustering with ConsensusClusterPlus R package v.1.52.0 (Wilkerson, M. D. & Hayes, D. N. ConsensusClusterPlus: a class discovery tool with confidence assessments and item tracking. Bioinformatics 26, 1572-1573 (2010)) with 10,000 permutations allowing from K=2 to K=7 groups, which robustly identified 3 consensus groups in both RRBS data types. Each sample was assigned a probability to belong to each of the groups (using the calcICL function). Samples where the maximum probability was below 0.5 or where 2 epitypes had a probability above 0.35 were considered as unclassified cases. In the 3 samples (2 RRBS-SE and 1 RRBS-PE) not included in the consensus matrices, the same strategy was used to find the CLL epitypes using the intersection of CpGs from both matrices used for consensus clustering (i.e., the 32-CpG and 153-CpG matrices for RRBS-SE and RRBS-PE data). In these cases, the epitype predictions were additionally verified using PCAs with all the shared CpGs with the rest of the samples, which further supported the assigned epitype.

Development of the epiCMIT Mitotic Clock for Next Generation Sequencing Data

[0361] The epigenetic mitotic clock, epiCMIT, was originally created with Illumina array data and thus is suitable for both 450k and EPIC arrays (Duran-Ferrer, M. et al. The proliferative history shapes the DNA methylome of B-cell tumors and predicts clinical outcome. Nature Cancer 1, 1066-1081 (2020)). The coverage of the original epiCMIT-CpGs based on Illumina 450k data in more targeted sequencing approaches like RRBS can be greatly compromised depending on the sequencing depth of samples or the enrichment towards particular regions of the genome. To overcome this, the epiCMIT-CpGs catalogue was expanded using high coverage whole genome bisulfite sequencing (WGBS) data from a previous publications including 15 samples covering the entire B-cell maturation spectrum (Kulis, M. et al. Whole-genome fingerprint of the DNA methylome during human B cell differentiation. Nat. Genet. 47, 746-756 (2015); Kretzmer, H. et al. DNA methylome analysis in Burkitt and follicular lymphomas identifies differentially methylated regions linked to somatic mutation and transcriptional control. Nat. Genet. 47, 1316-1325 (2015); Kulis, M. et al. Epigenomic analysis detects widespread gene-body DNA hypomethylation in chronic lymphocytic leukemia. Nat. Genet. 44, 1236-1242 (2012)). Briefly, the genome was segmented into 12 CHMM states with 200 bp resolution using the CHMM software (Ernst, J. & Kellis, M. ChromHMM: automating chromatin-state discovery and characterization. Nat. Methods 9, 215-216 (2012)) fed with 6 histone marks including H3K27ac, H3K4mel, H3K4me3, H3K36me3, H3K9me3 and H3K27me3 available for 15 normal and 16 neoplastic B cell samples. Normals included 6 naive B cells, 3 germinal-center B cells, 2 memory B cells and 3 tonsillar plasma cell samples. Neoplasia samples included 5 mantle cell lymphoma, 7 CLL and 4 multiple myeloma samples. These 12 chromatin states were ActProm (active promoter, with H3K27ac and H3K4me3), WkProm (weak promoter, with H3K4me1 and H3K4me3), PoisProm (poised promoter, with H3K27me3, H3K4me1 and H3K4me3), StrEnhl (strong enhancer 1, with H3K27ac, H3K4me1 and H3K4me3), StrEnh2 (strong enhancer 2, with H3K27ac and H3K4mel), WkEnh (weak enhancer, with H3K4mel), TxnTrans (transcription transition, with H3K36me3, H3K27ac and H3K4mel), TxnElong (transcription elongation, with H3K36me3), WkTxn (weak transcription, with low H3K36me3), H3K9me3 (H3K9me3-marked repressed heterochromatin), H3K27me3 (H3K27me3-marked repressed heterochromatin) and Het;LowSign (low-signal heterochromatin, with the absence of all six histone marks). Next, we selected CpGs located in repressive regions, including PoisProms, H3K27me3-repressed, H3K9me3 regions and Het;LowSign heterochromatin states. Afterwards, only CpGs showing extensive methylation differences (>0.5 difference in methylation fraction) between the lowly divided hematopoietic stem cell (HPC) and the highly divided bone-marrow plasma cells (bmPC) were retained, yielding 4,169 epiCMIT-hyper-CpGs (gaining methylation in H3K27me3 and PoisProm regions) and 808,872 epiCMIT-hypo-CpGs (CpGs losing methylation in H3K9me3 and Het;LowSign) in the hg38 genome assembly. Finally, the epiCMIT-hyper and epiCMIT-hypo scores were calculated as previously described (Duran-Ferrer, et al.) and the higher value in each sample was selected separately, which is different than the original strategy for Illumina array data where all samples shared the same epiCMIT-CpGs for the calculations (Duran-Ferrer, et al.) (only CpGs covered by at least 5 reads were used). This strategy was implemented to maximize the number of epiCMIT-CpGs in each sample, as only 124 and 311 epiCMIT-CpGs of the extended epiCMIT-CpGs catalogue were present in RRBS-SE and RRBS-PE consensus matrices, respectively. The new approach was validated using 24 samples profiled twice with different platforms, including 18 samples profiled with Illumina 450k and RRBS-PE, and 6 samples with RRBS-PE and RRBS-SE. In the samples profiled with Illumina 450k, the original epiCMIT-CpGs were used, whereas in RRBS data the available epiCMIT-CpGs was used in each sample of the extended catalogue of epiCMIT-CpGs based on WGBS data. These analyses showed that (i) the new epiCMIT approach was highly correlated with the original one, (ii) the epiCMIT could be calculated with varying numbers of epiCMIT-CpGs (with a minimum of around 800 epiCMIT-CpGs), and (iii) epiCMIT could be calculated with minimal impact due to different batches and platforms used. These statements were further supported by the PCA analyses with Illumina 450k data (ICGC cohort) and RRBS-SE data (DFCI and GCLLSG cohorts, n=93 and n=295, respectively) and RRBS-PE (data not shown), in which the epiCMIT gradient was similar in both platforms and unaffected by different cohorts.

H3K27Ac ChIP-Seq Analysis of Expression Clusters

[0362] To study the regulatory landscape of each ECs, previously analyzed cases with H3K27ac ChIP-seq were used (n=104), from which 70 cases had available RNA-seq and DNA methylation data. In these 70 samples, the number of cases for each expression cluster (EC) was: EC-m1=11, EC-ul=24, EC-m2=5, EC-o=2, EC-u2=5, EC-m3=10, EC-m4=12 and EC-i=1. From the 70 cases with available expression cluster (EC) classification, those expression clusters (ECs) with at least 5 cases (EC-o and EC-i were excluded) were selected and a differential analysis was performed using DESeq2 (Love, M. I., Huber, W. & Anders, S. Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. Genome Biol. 15, 550 (2014)) with raw H3K27ac counts. Genome-wide analyses was performed comparing each expression cluster (EC) versus the others using a consensus matrix with 100,640 regions showing at least one H3K27ac peak in one of the 104 samples, and those regions with an FDR<0.05 in any of the comparisons were retained.

[0363] Additionally, differential analyses was performed focused on those regulatory regions associated with the marker genes of each expression cluster (EC). To do so, all expression cluster (EC) marker gene coordinates were selected and extended 2,000 bp upstream of their corresponding transcription start sites. These regions were then intersected with the consensus matrix (n=100,640) and a differential DESeq2 (Love, M. I., Huber, W. & Anders, S. Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. Genome Biol. 15, 550 (2014)) analysis was performed with each expression cluster (EC) versus all the others and identified regions with FDR<0.05. These results were used for the H3K27ac annotation of the marker genes.

Statistical Methods

[0364] Unless otherwise stated, two-sided t-test was used for mean comparison and multiple testing was corrected to

compute false discovery rate (FDR, q) by the Benjamini-Hochberg procedure (Benjamini, Y. & Hochberg, Y. Controlling the false discovery rate: A practical and powerful approach to multiple testing. J. R. Stat. Soc. 57, 289-300 (1995)). Categorical enrichments were computed using a two-sided Fisher's Exact test unless otherwise stated.

Clinical Outcome Modeling

[0365] Failure-free survival (FFS) was calculated for treatment-naive patients as the time from the date of the sequenced sample to the date of first treatment ("natural progression"), progression (if the patient was sampled at the time of enrollment on a clinical trial) or death, and censored at the last known event-free date. In the genetics-focused analysis (Tables 1A-1E and 2A-2E), the first event was defined as time to next treatment in patients who received therapy within 30 days. Subset analysis included patients who were treatment-naive at the time of the sequenced sample and not enrolled on a therapeutic clinical trial; in this analysis, time between sample and date of first treatment was used. Overall survival (OS) was calculated as the time from the date of the sequenced sample to the date of death and censored at the date last known alive. Univariate and multivariable Cox regression models were constructed for each subset of data. Final models were selected using the glmnet function for regularized Cox regression using an elastic net penalty within the Coxnet package in R. Ten-fold cross-validation using the cv.glmnet function with a partial-likelihood deviance metric to minimize k was performed and the minimum CV-error model was used. The alpha was set to 1 corresponding to a Lasso penalty. The maximum iterations (maxit) parameter was set to 1000. Features identified as having non-zero coefficient values using elastic net and selected in the final model were then included in a Cox regression model to obtain the hazard ratios. These hazard ratios estimated the magnitude of effect but p-values and confidence intervals are not readily interpretable in the elastic net model and are therefore not reported. For the integrated analysis of all available datatypes variables including expression cluster and epitype categories were dummy coded. Prognostic significance of expression cluster and IGHV (heavy chain variable region of immunoglobulin genes) status were also considered using a chi-squared test with the difference in −2 log likelihood (−2logL) between models including somatic single nucleotide variants (sSNVs) and somatic copy number alterations (sCNAs). The Breslow approximation was used for handling ties in survival time.

Non-Coding Driver Discovery Procedure

[0366] MutSig2CV-NC (Rheinbay, E. et al. Analyses of non-coding somatic drivers in 2,658 cancer whole genomes. Nature 578, 102-111 (2020)) (github.com/broadinstitute/getzlab-PCAWG-MutSig2CV NC.git) was first used to identify candidate non-coding drivers in different genomic regions including enhancers, 3' UTRs, 5' UTRs, promoters and lncRNA genes. Then the stringent post-filtering steps described in detail in the Pan-cancer Analysis of Whole Genomes (PCAWG) Project's non-coding drivers paper (Bailey, et al) was followed on the candidate targets (q<0.5). In summary, the post-filters required:

[0367] 1). at least three mutations are present in the candidate driver;

[0368] 2). at least three patients have mutations in the candidate driver;

[0369] 3). less than 50% of mutations are in palindromic DNA;

[0370] 4). more than 50% of mutations are in mappable regions;

[0371] 5). less than 35% of mutations have Activation-induced cytidine deaminase (AID)-related signatures attribution greater than 50%; or

[0372] 6). mutations pass manual review in IGV.

[0373] For candidate targets failing any of the above filters, their p-values were re-assigned to be 1. Finally, Benjamini-Hochberg multiple hypothesis correction was applied on the corrected p-values to get the post-filtered q-values. This provided 1 candidate (q<0.1): WDR74 which was reported in the aforementioned PCAWG paper (Rheinbay, et al). Additionally, RNA-seq analysis of mutated versus unmutated samples did not reveal a notable effect on gene expression of mutations in an extended list of candidate genes. Thus, novel non-coding drivers were not reported.

Mutational Signatures Review

[0374] By applying SignatureAnalyzer (Kim, J. et al. Somatic ERCC2 mutations are associated with a distinct genomic signature in urothelial tumors. Nat. Genet. 48, 600-606 (2016)) to 177 WGS, 8 mutational signatures were observed acting in these samples. A careful review suggested that three signatures (S5, S7, S8) might correspond to possible sequencing artifacts, and thus were removed from the main signatures plot depicting the 5 biological mutational processes identified by SignatureAnalyzer. Specifically, the cosine similarity between S5 and SBS51 (per COSMIC v3.1) is 0.82, while the cosine similarity between S8 and SBS50 (per COSMIC v3.1) is 0.74. S7 only contains one striking peak at G(T>G)G motif and thus it is assumed to be a bleed-through artifact.

OTHER EMBODIMENTS

[0375] From the foregoing description, it will be apparent that variations and modifications may be made to the invention described herein to adapt it to various usages and conditions. Such embodiments are also within the scope of the following claims.

[0376] The recitation of a listing of elements in any definition of a variable herein includes definitions of that variable as any single element or combination (or subcombination) of listed elements. The recitation of an embodiment herein includes that embodiment as any single embodiment or in combination with any other embodiments or portions thereof.

[0377] All patents and publications mentioned in this specification are herein incorporated by reference to the same extent as if each independent patent and publication was specifically and individually indicated to be incorporated by reference. The disclosure may be related to PCT/US2021/045144, filed Aug. 9, 2021, the disclosure of which is incorporated herein by reference in its entirety for all purposes.

What is claimed is:

1. A method of treating a selected subject having chronic lymphocytic leukemia (CLL), the method comprising administering one of the following agents to the subject, wherein the subject is selected as sensitive to the agent by having a corresponding feature selected from EC-i, EC-m1, EC-m2, EC-m3, EC-m4, EC-o, EC-ul, EC-u2, M-CLL, U-CLL or from one of the following:

Agent	Feature	Direction
AZD5991	EC-i	Sensitive
Azacitidine	CARD11	Sensitive
Cerdulatinib	loss_13q14.13	Sensitive
GSK690693	i-CLL	Sensitive
Rapamycin	i-CLL	Sensitive
Rapamycin	EC-m4	Sensitive
Rapamycin	M-CLL	Sensitive
Umbralisib	M-CLL	Sensitive
Trametinib	CHD2	Sensitive
Bendamustine	loss_12p13.31a	Sensitive
Bendamustine	loss_5p15.33	Sensitive
Bendamustine	loss_7p22.2	Sensitive
Bendamustine	loss_14q32.12	Sensitive
Cerdulatinib	loss_13q14.3	Sensitive
Cerdulatinib	loss_13q14.13	Sensitive
JQ1	FBXW7	Sensitive
Navitoclax	M-CLL	Sensitive
Rapamycin	M-CLL	Sensitive
Ruxolitinib	loss_13q14.3	Sensitive
Venetoclax	loss_13q14.3	Sensitive
AZD5991	loss_3p13	Sensitive
Cerdulatinib	loss_13q14.3	Sensitive
Cerdulatinib	loss_13q14.13	Sensitive
Entospletinib	tri_12	Sensitive
GSK690693	i-CLL	Sensitive
JQ1	EC-i	Sensitive
Selinexor	MYD88	Sensitive
Trametinib	CHD2	Sensitive
Vorinostat	EC-m2	Sensitive

2. A method of treating a sensitive subject having chronic lymphocytic leukemia (CLL), the method comprising:

administering an agent to the sensitive subject, wherein the subject's sensitivity is determined by identifying the presence of a feature selected from EC-i, EC-m, EC-m2, EC-m3, EC-m4, EC-o, EC-ul, EC-u2, or from among the following expression subtypes, drives, genetic alterations, or CLL subtypes, or electing not to administer an agent to a resistant subject wherein the subject's resistance is determined by identifying the presence of a feature selected from EC-i, EC-m, EC-m2, EC-m3, EC-m4, EC-o, EC-ul, EC-u2, or from among the following expression subtypes, drives, genetic alterations, or CLL subtypes, wherein the agent, feature, and sensitivity or resistance includes:

Agent	Feature	Direction
A-1331852	EC-m2	Resistant
AZD5991	EC-i	Sensitive
Azacitidine	CARD11	Sensitive
Cerdulatinib	loss_13q14.13	Sensitive
GSK690693	i-CLL	Sensitive
Gandotinib	EC-i	Resistant
Navitoclax	EC-m2	Resistant
Nutlin-3	priortrt_Post	Resistant
Nutlin-3	FBXW7	Resistant
Rapamycin	EC-u1	Resistant
Rapamycin	i-CLL	Sensitive

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Rapamycin	U-CLL	Resistant
Rapamycin	EC-m4	Sensitive
Rapamycin	n-CLL	Resistant
Rapamycin	M-CLL	Sensitive
Umbralisib	U-CLL	Resistant
Umbralisib	n-CLL	Resistant
Umbralisib	M-CLL	Sensitive
Venetoclax	EC-m2	Resistant
Rapamycin	n-CLL	Resistant
Trametinib	CHD2	Sensitive
Bendamustine	loss_12p13.31a	Sensitive
Bendamustine	loss_5p15.33	Sensitive
Bendamustine	loss_7p22.2	Sensitive
Bendamustine	loss_14q32.12	Sensitive
Cerdulatinib	loss_13q14.3	Sensitive
Cerdulatinib	loss_13q14.13	Sensitive
Gandotinib	EC-i	Resistant
JQ1	FBXW7	Sensitive
MK-2206	priortrt_Post	Resistant
Navitoclax	U-CLL	Resistant
Navitoclax	n-CLL	Resistant
Navitoclax	M-CLL	Sensitive
Nutlin-3	priortrt_Post	Resistant
Rapamycin	U-CLL	Resistant
Rapamycin	M-CLL	Sensitive
Ruxolitinib	loss_13q14.3	Sensitive
Venetoclax	loss_13q14.3	Sensitive
AZD5991	loss_3p13	Sensitive
Cerdulatinib	loss_13q14.3	Sensitive
Cerdulatinib	loss_13q14.13	Sensitive
Entospletinib	tri_12	Sensitive
GSK690693	i-CLL	Sensitive
JQ1	EC-i	Sensitive
Rapamycin	n-CLL	Resistant
Selinexor	MYD88	Sensitive
Trametinib	CHD2	Sensitive
Vorinostat	EC-m4	Resistant
Vorinostat	EC-m2	Sensitive

drug	feature	direction
A-1331852	EC-m2	Resistant
AZD5991	EC-i	Sensitive
Azacitidine	CARD11	Sensitive
Cerdulatinib	loss_13q14.13	Sensitive
GSK690693	i-CLL	Sensitive
Gandotinib	EC-i	Resistant
Navitoclax	EC-m2	Resistant
Nutlin-3	priortrt_Post	Resistant
Nutlin-3	FBXW7	Resistant
Rapamycin	EC-u1	Resistant
Rapamycin	i-CLL	Sensitive
Rapamycin	U-CLL	Resistant
Rapamycin	EC-m4	Sensitive
Rapamycin	n-CLL	Resistant
Rapamycin	M-CLL	Sensitive
Umbralisib	U-CLL	Resistant
Umbralisib	n-CLL	Resistant
Umbralisib	M-CLL	Sensitive
Venetoclax	EC-m2	Resistant
Rapamycin	n-CLL	Resistant
Trametinib	CHD2	Sensitive
Bendamustine	loss_12p13.31a	Sensitive
Bendamustine	loss_5p15.33	Sensitive
Bendamustine	loss_7p22.2	Sensitive
Bendamustine	loss_14q32.12	Sensitive
Cerdulatinib	loss_13q14.3	Sensitive
Cerdulatinib	loss_13q14.13	Sensitive
Gandotinib	EC-i	Resistant
JQ1	FBXW7	Sensitive
MK-2206	priortrt_Post	Resistant
Navitoclax	U-CLL	Resistant
Navitoclax	n-CLL	Resistant
Navitoclax	M-CLL	Sensitive
Nutlin-3	priortrt_Post	Resistant

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Rapamycin	U-CLL	Resistant
Rapamycin	M-CLL	Sensitive
Ruxolitinib	loss_13q14.3	Sensitive
Venetoclax	loss_13q14.3	Sensitive
AZD5991	loss_3p13	Sensitive
Cerdulatinib	loss_13q14.3	Sensitive
Cerdulatinib	loss_13q14.13	Sensitive
Entospletinib	tri_12	Sensitive
GSK690693	i-CLL	Sensitive
JQ1	EC-i	Sensitive
Rapamycin	n-CLL	Resistant
Selinexor	MYD88	Sensitive
Trametinib	CHD2	Sensitive
Vorinostat	EC-m4	Resistant
Vorinostat	EC-m2	Sensitive
A-1331852	EC-m2	Resistant
AZD5991	EC-i	Sensitive
Azacitidine	CARD11	Sensitive
Cerdulatinib	loss_13q14.13	Sensitive
GSK690693	i-CLL	Sensitive
Gandotinib	EC-i	Resistant
Navitoclax	EC-m2	Resistant
Nutlin-3	priortrt_Post	Resistant
Nutlin-3	FBXW7	Resistant
Rapamycin	EC-u1	Resistant
Rapamycin	i-CLL	Sensitive
Rapamycin	U-CLL	Resistant
Rapamycin	EC-m4	Sensitive
Rapamycin	n-CLL	Resistant
Rapamycin	M-CLL	Sensitive
Umbralisib	U-CLL	Resistant
Umbralisib	n-CLL	Resistant
Umbralisib	M-CLL	Sensitive
Venetoclax	EC-m2	Resistant
Rapamycin	n-CLL	Resistant
Trametinib	CHD2	Sensitive
Bendamustine	loss_12p13.31a	Sensitive
Bendamustine	loss_5p15.33	Sensitive
Bendamustine	loss_7p22.2	Sensitive
Bendamustine	loss_14q32.12	Sensitive
Cerdulatinib	loss_13q14.3	Sensitive
Cerdulatinib	loss_13q14.13	Sensitive
Gandotinib	EC-i	Resistant
JQ1	FBXW7	Sensitive
MK-2206	priortrt_Post	Resistant
Navitoclax	U-CLL	Resistant
Navitoclax	n-CLL	Resistant
Navitoclax	M-CLL	Sensitive
Nutlin-3	priortrt_Post	Resistant
Rapamycin	U-CLL	Resistant
Rapamycin	M-CLL	Sensitive
Ruxolitinib	loss_13q14.3	Sensitive
Venetoclax	loss_13q14.3	Sensitive
AZD5991	loss_3p13	Sensitive
Cerdulatinib	loss_13q14.3	Sensitive
Cerdulatinib	loss_13q14.13	Sensitive
Entospletinib	tri_12	Sensitive
GSK690693	i-CLL	Sensitive
JQ1	EC-i	Sensitive
Rapamycin	n-CLL	Resistant
Selinexor	MYD88	Sensitive
Trametinib	CHD2	Sensitive
Vorinostat	EC-m4	Resistant
Vorinostat	EC-m2	Sensitive

3. The method of claim **1**, wherein Ec-i comprises an increase in one or more of GRIK3, IQGAP2, FCER1G, STK32B, GADD45A, ITGAX, KLF3, RFTN1, PTK2, DFNB31, and ZMAT1 polypeptides, or nucleic acid molecules encoding said polypeptides;

wherein EC-m1 comprises an increase in one or more of TFEC, COL18A1, SLC19A1, NRIP1, KCNH2, P2RX1, ARRDC5, BEX4, and APP polypeptides, or nucleic acid molecules encoding said polypeptide;

wherein EC-m2 comprises an increase in one or more of EML6, HCK, CD1C, VPS37B, CYBB, NXPH4, BTNL9, KLRK1, IQSEC1, BANKI, LEF1, SH3D21, FMOD, SEMA4A, CTLA4, ADTRP, IGSF3, IGFBP4, PDGFD, and APOD polypeptides, or nucleic acid molecules encoding said polypeptide;

wherein EC-m3 comprises an increase in MS4A4E, MYL9, NT5E, MS4A6A, PITPNC1, CNTNAP2, IGF2BP3, WNT3, CLDN7, TCF7, BASP1, FLJ20373, MAP4K4, LRRK2, SAMSN1, CEACAMI, TNFRSF13B, PHF16, MID1IPI, and ABCA9 polypeptides or nucleic acid molecules encoding said polypeptides;

wherein EC-m4 comprises an increase in MYBL1, NUGGC, GNG8, AEBP1, HIP1R, LATS2, RIMKLB, EML6, FADS3, MBOAT1, LCN10, DCLK2, and GLUL polypeptides or nucleic acid molecules encoding said polypeptide;

wherein EC-o comprises ACSM3, TOX2, PHF16, SESN3, TBC1D9, PIP5K1B, SIK1, DUSP5, GNG7, HIVEP3, MARCKSL1, GPR183, HRK, and PITPNC1, or nucleic acid molecules encoding said polypeptides;

wherein EC-ul comprises an increase in SEPT10, LDOC1, LPL, KANK2, SOWAHC, DUSP26, OSBPL5, WNT9A, FGFR1, GTSF1L, ADD3, AKT3, COBLL1, MNDA, FCRL3, FAM49A, FCRL2, SLC2A3, and MARCKS polypeptides, or nucleic acid molecules encoding said polypeptide; or

wherein EC-u2 comprises ITGB5, BCL7A, PPP1R9A, TSPAN13, SLC12A7, SSBP3, VASH1, SPG20, IL13RA1, NR3C2, TUBG2, ZNF804A, and IL2RA polypeptides, or nucleic acid molecules encoding said polypeptides.

4. The method of claim **3**, wherein levels of the polypeptide and polynucleotide are increased.

5. The method of claim **1**, wherein a subject having a characterized CLL is treated as follows:

M-CLL is treated with navitoclax, nutlin-3, duvelisib, ibrutinib, or venetoclax; or

U-CLL is treated with navitoclax, nutlin-3, duvelisib, ibrutinib, dasatinib, venetoclax, or idelasib.

6. The method of claim **1**, wherein venetoclax is administered in combination with an MCL1 inhibitor.

7. The method of claim **1**, wherein a subject having a characterized CLL is treated as follows:

EC-m3 is treated with venetoclax in combination with an MCL1 inhibitor;

EC-m2, M-CLL, and having a trisomy-12 driver is administered zanubrutinib; or

EC-i is administered abexinostat.

8. The method of claim **1**, wherein a subject receiving venetoclax is also administered one or more of the following: abexinostat, navitoclax, cerdulatinib, AZD5991, atorvastatin, zanubrutinib, GSK690693, trametinib, ponatinib, bendamustine, nutlin-3, and rapamycin.

9. The method of claim **1**, wherein a subject receiving venetoclax is administered two or more of the following: navitoclax, abexinostat, dasatinib, idelaslisib, duvelisib, cerdulatinib, bendamustine, GSK690693, nirogacestat, trametinib, and rapamycin.

10. The method of claim **1**, wherein a subject having the following expression subtype is treated as follows:

EC-i expression subtype, the method comprising administering to the subject navitoclax;

EC-m1 expression subtype, the method comprising administering to the subject nutlin-3, navitoclax, or cerdulatinib;

EC-m2 expression subtype, the method comprising administering to the subject abexinostat, duvelisib, idelalisib, entospletinib, or vorinostat;

EC-m3 expression subtype, the method comprising administering to the subject venetoclax, navitoclax, or Abexinostat;

EC-m4 expression subtype, the method comprising administering to the subject navitoclax, nutlin-3, or gandotinib; or

EC-o expression subtype, the method comprising administering to the subject gandotinib, abexinostat, or cerdulatinib;

EC-ul expression subtype, the method comprising administering to the subject gandotinib;

EC-u2 expression subtype, the method comprising administering to the subject ibrutinib, A-1331852, navitoclax, or rapamycin;

M-CLL subtype, the method comprising administering to the subject navitoclax or abexinostat; or

U-CLL subtype, the method comprising administering to the subject A-1331852, 25 atorvastatin, AZD5991, bendamustine, onalespib, trametinib, voruciclib, or zanubrutinib.

11. The method of claim **1**, wherein venetoclax is administered in combination with an MCL1 inhibitor selected from the group consisting of AZD5991, tapotoclax, MIK665, A-1210477, ANJ810, PRT1419, AS00491, APG-3526, CT-03, and CPT-628.

12. The method of claim **1**, wherein the subject is selected as comprising a driving alteration, wherein the driving alteration is:

(a) in a gene encoding a polypeptide selected from the group consisting of ATM, CARD11, CHD2, FBXW7, ITIH2, NOTCH1, NRAS, POT1, SF3B1, TP53, and ZMYM3; or

(b) in a genomic region selected from the group consisting of 7922.1, 15q24.2, 16pl1.2, 19pl3.3, 1921.3, 1942.13, 2p11.2, 2q31.1, 3p21.31, 3pl3, 5pl5.33, 7p22.2, 9q34.3, 1Op12.2, 10q24.2, 10q24.32, 11q22.3, 12pl3.31a, 13q14.13, 13q14.3, 14q32.12, 16q22.1, 17pl3.3, 17p13.1, and chromosome 12, and/or 2p.

13. The method of claim **1**, wherein CLL is further characterized as having:

i. a mutated (M-CLL) or unmutated IGHV (U-CLL) subtype;

ii. an expression subtype selected from EC-i, EC-m1, EC-m2, EC-m3, EC-m4, EC-o, EC-ul, or EC-u2; and/or

iii. a driving alteration in a gene encoding a polypeptide selected from the group consisting of ATM, CARD11, CHD2, FBXW7, ITIH2, NOTCHI, NRAS, POT1, SF3B1, TP53, and ZMYM3; and/or

iv. a driving alteration in a genomic region selected from the group consisting of 7q22.1, 15q24.2, 16pl1.2, 19pl3.3, 1921.3, 1942.13, 2pl1.2, 2q31.1, 3p21.31, 3pl3, 5p15.33, 7p22.2, 9q34.3, 1Op12.2, 10q24.2, 10q24.32, 11q22.3, 12p13.31a, 13q14.13, 13q14.3, 14q32.12, 16q22.1, 17pl3.3, 17pl3.1, chromosome 12, and 2p; and

wherein the agent has a delta priming value listed in FIG. **14** greater than 15 associated with the CLL subtype or driving alteration.

14. The method of claim **1**, further comprising characterizing the CLL as having:

i. a mutated (M-CLL) or unmutated IGHV (U-CLL) subtype;

ii. an expression subtype selected from EC-i, EC-m1, EC-m2, EC-m3, EC-m4, EC-o, EC-ul, or EC-u2; and/or

iii. a driving alteration in a gene encoding a polypeptide selected from the group consisting of ATM, CARD11, CHD2, FBXW7, ITIH2, NOTCHI, NRAS, POT1, SF3B1, TP53, and ZMYM3; and/or

iv. a driving alteration in a genomic region selected from the group consisting of 7q22.1, 15q24.2, 16pl1.2, 19pl3.3, 1921.3, 1942.13, 2pl1.2, 2q31.1, 3p21.31, 3pl3, 5pl5.33, 7p22.2, 9q34.3, 1Op12.2, 10q24.2, 10q24.32, 11q22.3, 12p13.31a, 13q14.13, 13q14.3, 14q32.12, 16q22.1, 17pl3.3, 17pl3.1, chromosome 12, and 2p; and

(b) selecting the subject for inclusion in the clinical trial if the agent has a positive delta priming value of greater than 15 listed in FIG. **14** for the subtype and/or driving alteration of the CLL, and otherwise excluding the subject from the clinical trial.

15. The method of claim **14**, wherein the driving alteration to the genomic region is a duplication or a deletion.

16. A combination therapeutic comprising venetoclax and an agent having a delta priming value listed in FIG. **14** greater than 15, abexinostat, navitoclax, cerdulatinib, AZD5991, atorvastatin, zanubrutinib, GSK690693, trametinib, ponatinib, bendamustine, nutlin-3, and rapamycin, or a MCL1 inhibitor.

17. The combination therapeutic of claim **16**, wherein venetoclax and the agent are formulated separately.

18. The combination therapeutic of claim **16**, wherein venetoclax and the agent are administered concurrently.

19. The combination therapeutic of claim **16**, wherein venetoclax and the agent are administered sequentially within at least about 1, 3, 6, 9, 12, or 24 hours of one another.

20. The combination therapeutic of claim **16**, wherein the MCL1 inhibitor is selected from the group consisting of AZD5991, tapotoclax, MIK665, A-1210477, ANJ810, PRT1419, AS00491, APG-3526, CT-03, and CPT-628.

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