

Figure S1 Distribution of DNA fragment. (A-C) Fragmentomic metric changes between pre-treatment and on-treatment samples are shown according to the proportion of fragments in P1 (A), the proportion of fragments in P2 (B), and the fragmentation ratio (C), for both the PeR and non-PeR groups. Only the patients with sufficient sample for fragmentomic analysis (n=26) were studied. Statistical significance was calculated by performing a two-sided paired t-test. (D-F) Fold-changes in fragmentomic metrics (pre-treatment values divided by on-treatment values) were compared between the PeR and non-PeR groups, according to the proportion in P1 (D), proportion in P2 (E), and the fragmentation ratio (F). Statistical significance was calculated by performing the Wilcoxon rank sum exact test. *, P<0.05. PeR, persistent response; NS, not significant.

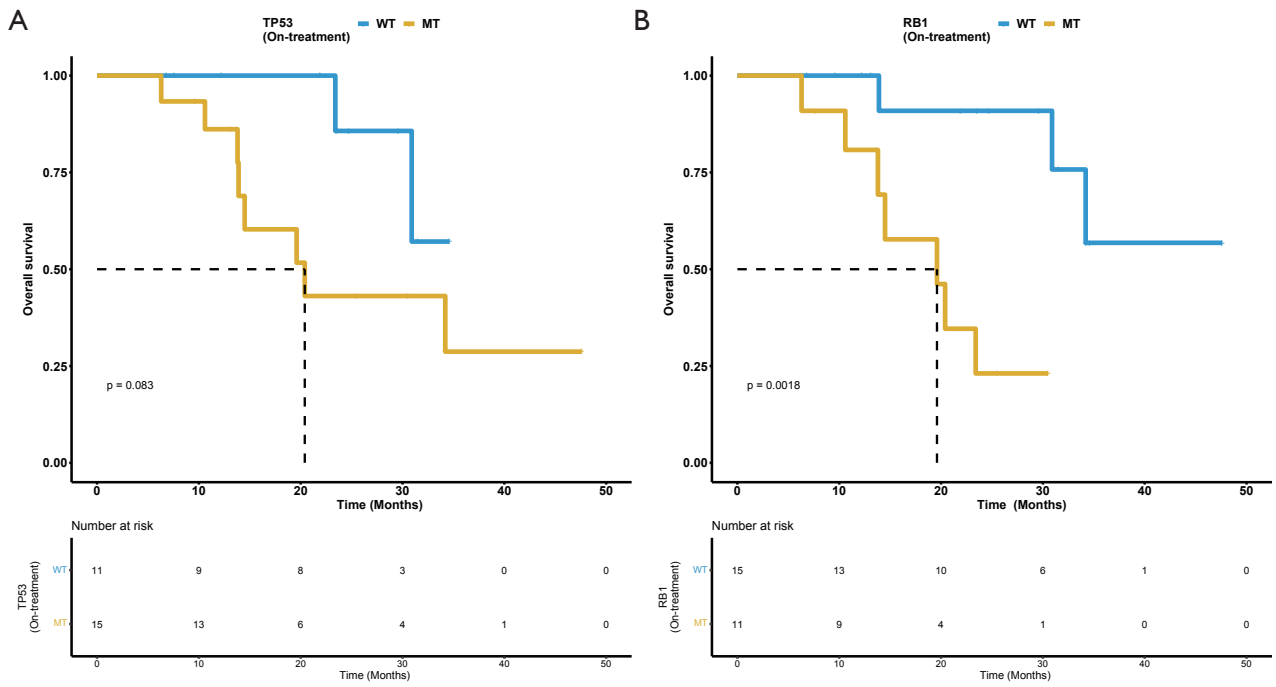


Figure S2 Survival analysis based on mutation profile. (A,B) Kaplan-Meier curves comparing the overall survival trends according to the *TP53* mutation status (A) and the *RB1* mutation status (B) in the on-treatment samples. Statistical significance was calculated by performing the log-rank test. WT, wild-type; MT, mutation.

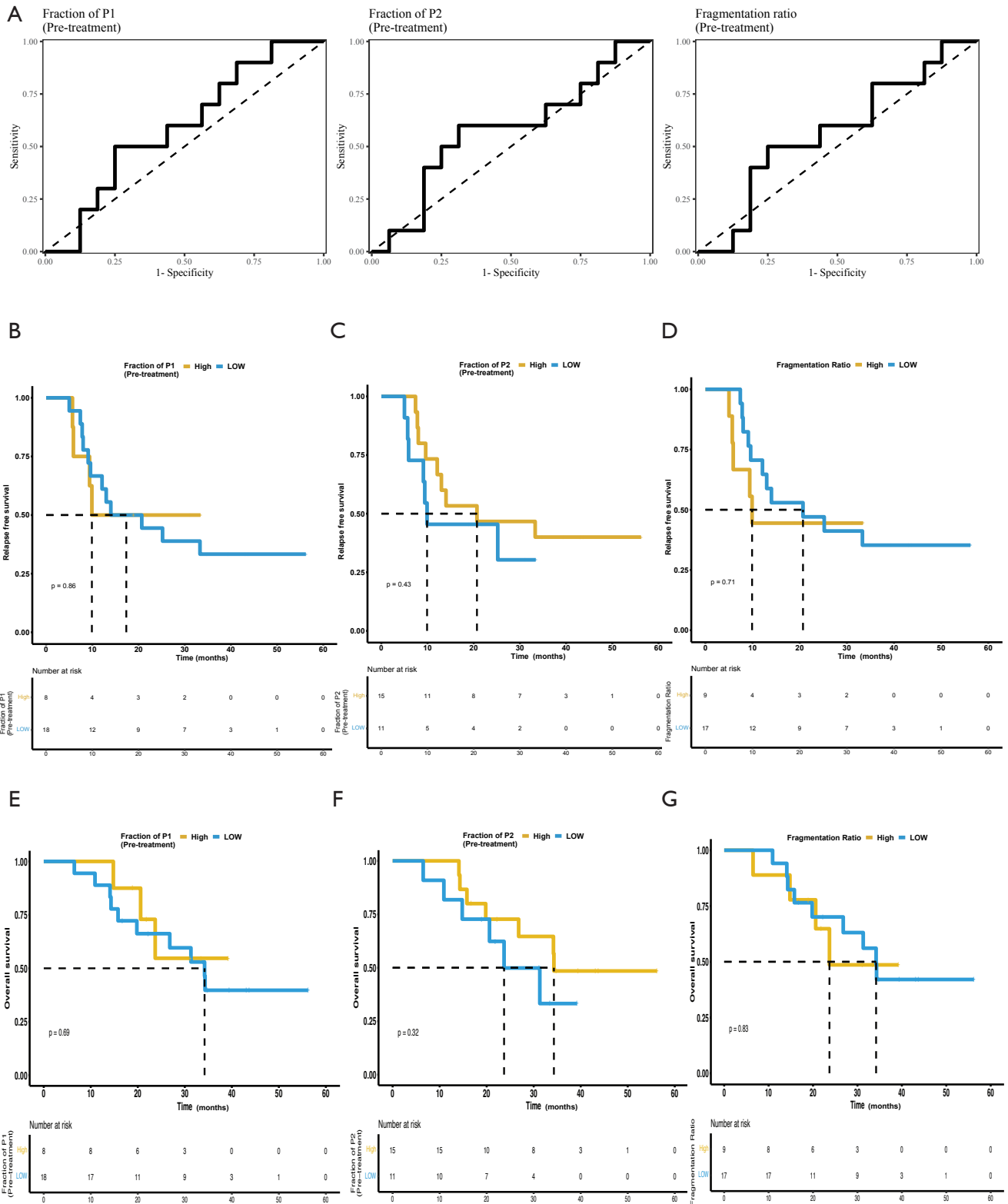


Figure S3 Predictive value and survival analysis based on fragmentomic analysis. (A) Use of ROC curves to distinguish the non-PeR group from the PeR group, based on the fraction of fragments in P1 (left), fraction in P2 (middle), and fragmentation ratio (right) in pre-treatment samples. (B-D) Kaplan-Meier curve showing differences in the RFS trend, according to the fraction of fragments in P1 (B), the fraction in P2 (C), and the fragmentation ratio (high group vs. low group) (D) in the pre-treatment samples. The overall survival according to the fraction of fragments in P1 (E), the fraction in P2 (F), and the fragmentation ratio (high group vs. low group) (G) in the pre-treatment samples. The optimal cut-off value (showing a maximum sum of the sensitivity and specificity) from the ROC analysis was used to define the high- and low-fragmentation groups. ROC, receiver operating characteristic; PeR, persistent response; RFS, relapse-free survival.

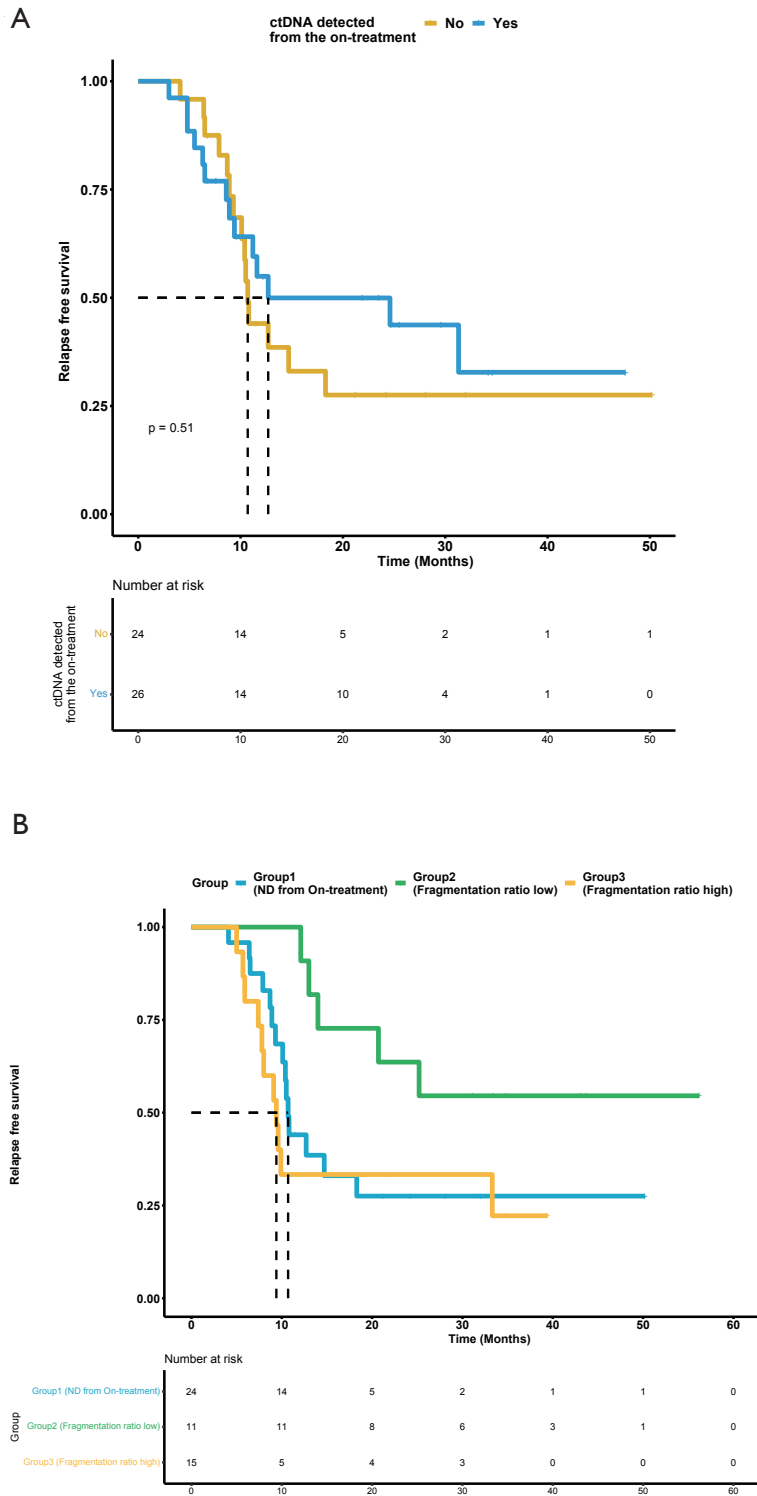


Figure S4 Survival analysis based on the presence of ctDNA. (A) Kaplan-Meier curve analysis was performed to compare RFS differences according to the presence of detectable ctDNA in all on-treatment samples. (B) Kaplan-Meier curve analysis was extended to further divide the ctDNA-positive group into groups with low and high fragmentation ratios. ctDNA, circulating tumor DNA; RFS, relapse-free survival; ND, not detected.

Table S1 Overall sequencing outcome

Tube ID	Type	Input DNA (ng)	Raw bases	Mapped read ratio	On-target read ratio	On-target mean depth	Fragment mean depth
TG-100	cfDNA	19.40	21,875,473,586	99.96	68.34	26,003	2,583
TG-105	cfDNA	11.55	22,469,576,442	99.98	64.58	24,875	1,882
TG-106	cfDNA	20.00	14,214,167,862	99.97	67.82	16,144	2,165
TG-109	cfDNA	20.00	16,190,379,456	99.97	66.95	18,551	2,431
TG-111	cfDNA	20.00	14,066,987,256	99.96	66.38	16,466	2,157
TG-113	cfDNA	20.00	16,015,908,922	99.97	64.36	17,617	2,274
TG-117	cfDNA	20.00	15,073,574,396	99.97	64.02	16,331	2,037
TG-118	cfDNA	20.00	16,125,403,854	99.97	65.40	17,908	2,359
TG-120	cfDNA	15.44	16,513,294,768	99.97	68.42	19,564	1,905
TG-123	cfDNA	20.00	15,486,157,434	99.95	67.63	18,345	2,126
TG-124	cfDNA	19.92	19,592,530,558	99.91	69.44	24,122	2,109
TG-128	cfDNA	20.00	16,594,651,152	99.92	69.37	19,988	1,913
TG-131	cfDNA	20.00	15,157,966,182	99.96	71.34	19,140	1,653
TG-132	cfDNA	20.00	17,097,157,106	99.96	70.85	21,398	2,310
TG-133	cfDNA	20.00	23,908,758,650	99.96	69.77	28,563	2,586
TG-135	cfDNA	20.00	15,437,435,472	99.97	68.34	17,826	2,391
TG-138	cfDNA	20.00	15,150,955,252	99.97	69.72	18,444	1,790
TG-144	cfDNA	20.00	15,218,008,614	99.96	68.63	18,135	2,038
TG-149	cfDNA	20.00	16,319,347,046	99.97	61.64	17,086	1,522
TG-154	cfDNA	11.93	25,161,599,610	99.97	66.75	28,663	1,582
TG-159	cfDNA	18.34	15,482,341,362	99.97	63.73	16,770	1,550
TG-167	cfDNA	9.15	18,601,199,552	99.96	66.10	21,180	911
TG-171	cfDNA	20.00	22,348,434,578	99.95	65.60	24,959	2,230
TG-174	cfDNA	20.00	18,443,345,964	99.92	67.02	21,832	1,207
TG-180	cfDNA	14.82	18,720,332,210	100.00	68.56	20,897	1,627
TG-183	cfDNA	20.00	21,912,791,424	99.96	67.18	25,680	2,231
TG-192	cfDNA	20.00	15,783,073,566	99.96	70.91	20,152	2,021
TG-207	cfDNA	20.00	22,049,579,304	99.96	67.45	25,374	1,642
TG-211	cfDNA	15.08	14,578,311,006	99.95	51.33	12,972	1,209
TG-216	cfDNA	9.35	24,514,274,992	99.96	66.82	28,796	1,072
TG-220	cfDNA	20.00	18,963,855,044	99.95	70.50	23,497	2,286
TG-225	cfDNA	10.30	22,344,809,370	99.96	64.88	24,706	682
TG-229	cfDNA	20.00	21,068,152,388	99.96	70.10	25,555	2,519
TG-234	cfDNA	20.00	22,648,341,718	99.96	68.58	27,044	2,474
TG-237	cfDNA	20.00	22,891,925,254	99.96	69.37	27,587	2,431
TG-240	cfDNA	8.23	26,283,990,764	99.96	67.88	30,719	2,303
TG-241	cfDNA	20.00	19,476,547,156	99.95	68.21	23,438	2,148
TG-27	cfDNA	8.95	23,822,403,562	99.97	69.68	28,942	1,560
TG-32	cfDNA	12.65	21,142,287,952	99.97	68.81	25,399	1,960
TG-41	cfDNA	9.10	24,673,699,282	99.96	67.66	29,759	1,459
TG-46	cfDNA	20.00	18,170,454,234	99.93	67.35	21,099	1,937
TG-50	cfDNA	20.00	22,550,309,800	99.97	69.60	27,422	2,582
TG-53	cfDNA	20.00	20,678,036,036	99.97	66.86	24,096	2,615
TG-56	cfDNA	20.00	22,187,612,934	99.96	67.92	26,572	2,172
TG-70	cfDNA	10.67	19,412,250,148	99.96	70.01	23,627	1,641
TG-75	cfDNA	16.65	21,809,096,704	99.97	69.12	26,096	2,196
TG-78	cfDNA	20.00	14,392,397,994	99.96	70.00	17,423	2,095
TG-81	cfDNA	20.00	27,423,935,366	99.95	71.20	34,776	2,567
TG-88	cfDNA	20.00	20,828,213,690	99.95	65.91	24,315	1,355
TG-89	cfDNA	20.00	30,172,650,880	99.96	71.89	38,815	2,449
TG-105	PBMC	100.00	4,615,350,032	99.97	66.78	5,236	1,134
TG-106	PBMC	100.00	5,140,767,820	99.97	66.84	5,734	1,250
TG-109	PBMC	100.00	3,619,188,838	99.98	59.10	3,617	675
TG-117	PBMC	100.00	6,046,067,482	99.95	67.04	6,764	1,282
TG-132	PBMC	100.00	5,742,451,782	99.97	66.47	6,464	1,280
TG-135	PBMC	100.00	6,274,924,894	99.98	71.21	7,620	1,223
TG-159	PBMC	100.00	2,635,580,274	99.94	42.60	1,583	300
TG-167	PBMC	100.00	4,615,595,256	99.97	43.51	3,400	813
TG-171	PBMC	100.00	4,778,947,056	99.95	53.85	4,200	1,007
TG-174	PBMC	100.00	4,141,415,392	99.96	47.51	3,348	758
TG-180	PBMC	100.00	3,229,113,860	99.96	51.97	2,873	642
TG-183	PBMC	100.00	3,469,187,552	99.93	30.80	1,611	359
TG-192	PBMC	100.00	4,729,592,102	99.98	51.25	4,168	839
TG-207	PBMC	100.00	4,692,485,362	99.95	52.51	4,049	886
TG-211	PBMC	100.00	4,178,295,028	99.96	53.82	3,786	913
TG-216	PBMC	100.00	5,927,249,508	99.97	49.48	4,847	1,148
TG-220	PBMC	100.00	4,865,896,782	100.00	70.34	5,488	1,219
TG-225	PBMC	100.00	4,890,691,888	99.96	51.27	4,164	1,023
TG-229	PBMC	100.00	4,450,169,622	100.00	69.77	4,969	950
TG-234	PBMC	100.00	4,627,283,562	100.00	70.50	5,201	1,135
TG-237	PBMC	100.00	4,562,846,124	100.00	70.61	5,115	1,164
TG-240	PBMC	100.00	4,987,836,832	100.00	71.01	5,658	1,188
TG-241	PBMC	100.00	4,695,340,168	100.00	70.82	5,320	1,044
TG-46	PBMC	100.00	5,130,100,576	99.97	63.90	5,504	1,134
TG-50	PBMC	100.00	6,603,324,828	99.98	66.74	7,331	1,560
TG-75	PBMC	100.00	5,588,937,028	99.97	68.05	6,454	1,275
TG-78	PBMC	100.00	6,706,195,994	99.97	67.16	7,570	1,433

Table S2 List of genes included in the sample

Target genes
<i>ABL1</i>
<i>AKT1</i>
<i>AKT2</i>
<i>ALK</i>
<i>APC</i>
<i>AR</i>
<i>ARAF</i>
<i>ARID1A</i>
<i>ATM</i>
<i>BRAF</i>
<i>BRCA1</i>
<i>BRCA2</i>
<i>BTK</i>
<i>CBL</i>
<i>CCND1</i>
<i>CCND2</i>
<i>CCNE1</i>
<i>CD274</i>
<i>CDH1</i>
<i>CDK4</i>
<i>CDK6</i>
<i>CDKN2A</i>
<i>CEBPA</i>
<i>CSF1R</i>
<i>CTNNB1</i>
<i>DDR2</i>
<i>DPYD</i>
<i>EGFR</i>
<i>ERBB2</i>
<i>ERBB3</i>
<i>ESR1</i>
<i>FBXW7</i>
<i>FGFR1</i>
<i>FGFR2</i>
<i>FGFR3</i>
<i>FLT3</i>
<i>GATA3</i>
<i>GNA11</i>
<i>GNAQ</i>
<i>GNAS</i>
<i>HRAS</i>
<i>IDH1</i>
<i>IDH2</i>
<i>IGF1R</i>
<i>JAK2</i>
<i>JAK3</i>
<i>KDM6A</i>
<i>KDR</i>
<i>KEAP1</i>
<i>KIT</i>
<i>KRAS</i>
<i>MAP2K1</i>
<i>MAP2K2</i>

Table S2 (continued)

Table S2 (continued)

Target genes
<i>MAPK1</i>
<i>MAPK3</i>
<i>MDM2</i>
<i>MET</i>
<i>MLH1</i>
<i>MPL</i>
<i>MSH2</i>
<i>MSH6</i>
<i>MTOR</i>
<i>MYC</i>
<i>MYCN</i>
<i>NF1</i>
<i>NF2</i>
<i>NFE2L2</i>
<i>NOTCH1</i>
<i>NPM1</i>
<i>NRAS</i>
<i>NTRK1</i>
<i>NTRK2</i>
<i>NTRK3</i>
<i>PDCD1LG2</i>
<i>PDGFRA</i>
<i>PDGFRB</i>
<i>PIK3CA</i>
<i>PIK3R1</i>
<i>PMS2</i>
<i>PPP2R1A</i>
<i>PTEN</i>
<i>PTPN11</i>
<i>RAF1</i>
<i>RB1</i>
<i>RET</i>
<i>RHEB</i>
<i>RHOA</i>
<i>RIT1</i>
<i>RNF43</i>
<i>ROS1</i>
<i>RUNX1</i>
<i>SETD2</i>
<i>SMAD4</i>
<i>SMO</i>
<i>STAG2</i>
<i>STK11</i>
<i>TCF7L2</i>
<i>TERT</i>
<i>TOP2A</i>
<i>TP53</i>
<i>TSC1</i>
<i>TSC2</i>
<i>U2AF1</i>
<i>UGT1A1</i>
<i>VHL</i>

Table S3 Comparison with the database included in cBioPortal

Database (cBioPortal)	Uncover	Total number of samples	Coverage
Small Cell Lung Cancer (CLCGP, <i>Nat Genet</i> 2012)	1	29	97%
Small Cell Lung Cancer (Johns Hopkins, <i>Nat Genet</i> 2012)	1	41	98%
Small Cell Lung Cancer (U Cologne, <i>Nature</i> 2015)	2	110	98%
Small-Cell Lung Cancer (Multi-Institute, <i>Cancer Cell</i> 2017)	0	10	100%

CLCGP, Clinical Lung Cancer Genome Project.