Table S1. Baseline demographic comparison between the WES and non-WES patients

	WES patients (60)	Others patients(64)	p value
liver met	38 (63.33%)	31 (48.44%)	0.1066 (exact test)
baseline tumor size (>= median)	29 (48.33%)	32 (50%)	0.8596 (exact test)
age (mean)	45.28	46.92	0.4044 (t test)
male	48 (80%)	47 (73.44%)	0.4056 (exact test)
distant met sites (mean)	2.03	1.998	0.9276 (rank sum test)
smoking (never)	42 (70%)	43 (67.19%)	1 (exact test)
ecog (1)	38 (63.33%)	51 (79.69%)	0.0484 (exact test)

Table S2. Response and survival outcomes.

Outcomes	**All patients (124)**
Objective response rate% (95% CI)	29.8 (21.8 - 37.9)
Disease control rate% (95% CI)	60.5 (51.9 – 69.1)
Best overall response, n (%)	
Complete response	2 (1.6)
Partial response	35 (27.4)
Stable disease	38 (30.6)
Progressive disease	49 (39.5)
Duration of response, months (95%CI)	9.5 (6.0 – 13.0)
Median PFS, months (95% CI)	3.8 (3.4 – 6)
Median time to response in responders, month (95% CI)	1.9 (1.8 – 2.6)
Median OS follow up time, month (95% CI)	24.7 (23.3 – 26.6)
Median OS, months (95% CI)*	17.1 (14.2 – 24.7)
OS Rate (95% CI) for all patients	
1 year	62.6 (54.5 - 71.9)
2 years	39.7 (31.5 – 50.0)

Table S3. Associations of baseline demographic and clinical characteristics with PFS and OS in multivariate analysis.

	PFS	OS

	HR	95% CI	*P*	HR	95% CI	*P*
Sex: Male vs Female	0.91	0.53-1.55	0.72	0.93	0.49-1.75	0.82
Age: <65 vs ≥65	1.61	0.55-4.71	0.39	2.13	0.49-9.34	0.37
Smoking: Never vs Former/Current	0.88	0.54-1.43	0.60	0.84	0.48-1.56	0.63
Comorbidity: Yes vs No	1.13	0.72-1.76	0.60	1.01	0.60-1.71	0.97
ECOG: 0 vs 1	1.21	0.76-1.94	0.42	1.28	0.72-2.29	0.63
Number of metastasis: ≥3 vs <3	1.53	0.93-2.51	0.09	1.72	0.96-3.08	0.07
Liver metastasis: Yes vs No	1.63	1.02-2.61	0.04	1.78	1.09-3.13	0.04
Prior radiation: Yes vs No	0.47	0.25-0.85	0.01	0.40	0.21-0.79	0.01
Prior line of therapy: ≥ 3 vs <3	1.38	0.91-2.11	0.13	1.51	0.93-2.46	0.10

PFS, progression free survival; OS, overall survival; HR, hazard ratio; CI, confident interval; ECOG, Eastern Cooperative Oncology Group;

Table S4. The distribution of copy number alteration in key immune-related pathways

pathway	n	pfs.p.val	pfs.hr	os.p.val	os.hr
granzyme	18	0.012	1.585	0.0046	2.385
gasdermins	8	0.39	1.429	0.016	2.66
Interferons	14	0.023	1.326705	0.00079	2.64593
Chemokine_Receptors	4	na	na	na	na
Antigen_Processing_and_Presentation	0	na	na	na	na
Antimicrobials	0	na	na	na	na
BCRSignalingPathway	0	na	na	na	na
Chemokines	1	na	na	na	na
Cytokines	1	na	na	na	na
Cytokine_Receptors	2	na	na	na	na
Interferon_Receptor	0	na	na	na	na
Interleukins	2	na	na	na	na

Interleukins_Receptor	0	na	na	na	na
NaturalKiller_Cell_Cytotoxicity	0	na	na	na	na
TCRsignalingPathway	0	na	na	na	na
TGFb_Family_Member	4	na	na	na	na
TGFb_Family_Member_Receptor	0	na	na	na	na
TNF_Family_Members	0	na	na	na	na
TNF_Family_Members_Receptors	2	na	na	na	na

Table S5. The CNVKit log2 depth ratio of GZMB and GZMH in the 60 patients

patient_id	log2 depth ratio		GZMB/GZMH status
	GZMB	GZMH	
p45	-0.36038	-0.56482	wild type
p11	-0.31966	-0.28237	wild type
p32	0.173343	0.115398	wild type
p6	-0.22267	-0.22475	wild type
p30	-0.02886	-0.10671	wild type
p37	-0.09512	-0.19327	wild type
p34	-0.25613	-0.27677	wild type
p20	0.134163	0.101876	wild type
p92	-0.17776	-0.3228	wild type
p31	-0.5556	-0.69587	loss
p41	-0.12289	-0.14288	wild type
p98	-0.16875	0.000115	wild type
p42	-0.07853	-0.04182	wild type
p101	-0.04892	-0.01543	wild type
p114	-0.23625	-0.38921	wild type
p25	-0.52762	-0.27203	wild type
p4	-0.46485	-0.27356	wild type
p115	-0.61871	-0.69547	loss
p116	0.060496	0.161406	wild type
p100	-0.35539	-0.11781	wild type
p16	-0.43394	-0.22966	wild type
p96	-0.59547	-0.60675	loss
p3	-0.73112	-0.45042	loss
p102	-0.23258	-0.09468	wild type
p104	-0.42502	-0.42223	wild type
p33	-0.19819	-0.06376	wild type
p29	-0.29134	-0.18515	wild type
p19	-0.47353	-0.5139	wild type
p2	-0.2507	-0.1256	wild type

p21	-0.28785	0.161817	wild type
p13	-0.5817	-0.6924	loss
p43	-0.70264	-0.82566	loss
p94	-0.52137	-0.86115	loss
p117	-0.89723	-0.52548	loss
p111	-0.37447	-0.4521	wild type
p27	-0.07491	-0.03292	wild type
p18	-0.81513	-0.67369	loss
p103	-0.04052	0.116346	wild type
p8	-0.32485	-0.40774	wild type
p39	-0.73978	-0.68099	loss
p9	-0.90251	-1.04794	loss
p40	-0.21799	-0.28888	wild type
p112	-0.1375	-0.26298	wild type
p93	-0.43087	-0.35952	wild type
p1	-0.48353	-0.32181	wild type
p10	-1.02525	-1.06066	loss
p17	-1.24858	-1.1727	loss
p26	-0.82483	-0.37267	loss
p36	-0.2527	-0.23136	wild type
p44	-0.2856	-0.21452	wild type
p38	-0.87997	-0.86822	loss
p24	-0.52393	-0.30101	wild type
p14	-0.0425	0.054351	wild type
p121	-0.17974	-0.16554	wild type
p7	-0.51911	-0.44645	wild type
p113	-0.78098	-0.46841	loss
p22	-0.92081	-0.78376	loss
p15	-0.20235	-0.2885	wild type
p35	-0.48295	-0.37992	wild type
p28	0.103037	-0.02006	wild type

Table S6.Mutations associated with PFS or OS. Only included genes that were mutated in 4 or more patients with p value <= 0.05 for either PFS or OS. P values were not adjusted due to the lack of significant adjusted p values.

gene	number	os.p.value	pfs.p.value
NOS1	4	0.962339777	0.73799623
OBSCN	7	**0.000316474**	0.082159409
IGKV1-8	5	**0.031433525**	0.206479752
CYLD	8	0.222307225	0.456730282
NBPF1	8	0.854442525	0.267454283
RERE	4	0.393358182	0.382176333

NFKBIA	9	0.65662569	**0.004955627**
KMT2D	7	0.197486622	0.46532678
MACF1	6	0.187139352	0.556847783
MUC4	6	**0.044041512**	0.693289075
CSMD3	5	0.119080011	0.450365447
FLG	4	0.784839515	0.526552508
MUC16	4	0.735146133	0.590091484
HSPG2	4	0.992552884	**2.21E-05**
TP53	6	0.226000419	0.957496029
CYP2A6	5	0.846540897	0.544816463
ANK3	4	0.749460708	0.659653543
DCHS1	4	0.5404297	0.791438639
SYNE1	4	0.83169395	0.785437023

Table S7. Gene level copy number loss associated with PFS or OS. Only deletion that occurred in 5 or more patients and with adjusted p value <= 0.05 for either PFS or OS were listed.

name	chrom	os.p.value	pfs.p.value	number.of.deletion	adjusted.pfs.p	adjusted.os.p
CDC25C	chr5	0.00366546	7.53E-06	5	0.003283215	0.03426812
INSL6	chr9	0.0062947	1.02E-05	7	0.003283215	0.0464844
GZMB	chr14	0.00021662	0.00010918	13	0.023509846	0.00551139
IL21	chr4	0.0074294	0.00019041	6	0.024601369	0.04999367
IFNE	chr9	0.01960387	0.00018263	10	0.024601369	0.08331643
FOXE1	chr9	0.00460438	0.00022967	28	0.024728305	0.03913723
CMTM8	chr3	6.47E-07	0.00027612	7	0.025481594	8.36E-05
NRG3	chr10	0.00820632	0.00043082	9	0.034788337	0.05197334
CRIP2	chr14	0.02455411	0.00050464	11	0.036222135	0.09695799
CSF2	chr5	0.03853706	0.00060821	10	0.039290446	0.12965922
SFTPD	chr10	8.94E-08	0.00085578	9	0.050257747	1.93E-05
LGMN	chr14	0.00149684	0.00136948	5	0.073723444	0.01824453
ERCC8	chr5	0.00093788	0.00173167	5	0.086050775	0.01442553
TAL1	chr1	0.00555154	0.00272038	7	0.110406726	0.04350908
CYSLTR2	chr13	2.61E-08	0.00468581	5	0.168168547	8.42E-06
DNAJC6	chr1	3.05E-07	0.00644401	7	0.169737291	4.92E-05
RASGRF2	chr5	4.69E-05	0.00749884	5	0.169737291	0.00252398
DEFB1	chr8	9.33E-05	0.00715683	5	0.169737291	0.00397137
SACS	chr13	0.00039169	0.00583438	5	0.169737291	0.00790724
CCNB1IP1	chr14	0.00045872	0.00697883	5	0.169737291	0.00800901
PCDHB7	chr5	0.0006673	0.00540352	15	0.169737291	0.01063431
TRHR	chr8	0.00559018	0.00756639	7	0.169737291	0.04350908
IFNA1	chr9	0.00173208	0.00884371	26	0.174667689	0.01963029
IL33	chr9	6.05E-05	0.00995083	9	0.183663845	0.00279346
PLEK2	chr14	1.50E-06	0.01198018	6	0.198440979	0.00012075
LMF1	chr16	0.00161432	0.01190101	7	0.198440979	0.0186223

UTS2	chr1	0.00067493	0.01448357	5	0.222771134	0.01063431
TCL1B	chr14	0.00017973	0.01967159	35	0.270379764	0.00515291
ERC2	chr3	0.00019144	0.01891198	6	0.270379764	0.00515291
DIO2	chr14	0.00018227	0.02122722	21	0.279744752	0.00515291
HAPLN1	chr5	0.00045683	0.02103361	7	0.279744752	0.00800901
NPAP1	chr15	0.00039063	0.02586062	32	0.312759297	0.00790724
SERPINB3	chr18	0.0065257	0.02614397	18	0.312759297	0.0464844
LMO1	chr11	0.00317531	0.02701697	7	0.317326579	0.03067506
WASF3	chr13	3.56E-05	0.02828509	20	0.321487133	0.00208894
TEK	chr9	0.00717783	0.02836651	11	0.321487133	0.04985889
TCL1A	chr14	0.0001079	0.03009866	30	0.32888079	0.0041002
PAX6	chr11	0.00143975	0.02980357	6	0.32888079	0.01823688
CCR8	chr3	0.00271586	0.03403386	12	0.32888079	0.02747003
BCRP2	chr22	0.00635247	0.03104317	10	0.32888079	0.0464844
GPC5	chr13	1.41E-09	0.03624524	13	0.339483454	9.10E-07
ADAM29	chr4	0.00207351	0.03626062	26	0.339483454	0.02232475
TLR2	chr4	0.00184195	0.03865021	5	0.356686197	0.02016774
PENK	chr8	0.00141482	0.04486092	14	0.395329269	0.01823688
HTR1A	chr5	0.00358363	0.04406449	26	0.395329269	0.03404448
EPHA3	chr3	3.08E-05	0.05122007	5	0.396240738	0.0019893
RNASE10	chr14	0.00414101	0.04782977	12	0.396240738	0.03715407
ERAS	chr23	0.00737108	0.05125172	5	0.396240738	0.04999367
SSX1	chr23	0.00043806	0.05849722	40	0.410752196	0.00800901
CHL1	chr3	0.00045152	0.06602406	22	0.435219797	0.00800901
EDNRB	chr13	1.16E-06	0.0691112	10	0.445646556	0.00010732
PRKCD	chr3	0.00470657	0.07744637	5	0.461684564	0.03948633
IL5	chr5	0.00689204	0.07704228	5	0.461684564	0.04839408
BMP3	chr4	0.00158018	0.08640592	9	0.481728348	0.01855999
PEG3	chr19	0.00532171	0.08845028	30	0.481728348	0.04313949
WNT7A	chr3	0.00029281	0.09804055	25	0.503277877	0.00700584
PTGER3	chr1	0.00318147	0.10049976	9	0.503277877	0.03067506
THRB	chr3	0.00015538	0.10648619	5	0.505971896	0.00515291
IFNA8	chr9	0.00226418	0.1065204	30	0.505971896	0.02397803
CHGA	chr14	0.00399635	0.1027006	36	0.505971896	0.03636112
TCL6	chr14	0.00641558	0.10623955	36	0.505971896	0.0464844
FAM19A4	chr3	0.0001899	0.1117801	30	0.51212726	0.00515291
HTN3	chr4	0.00013145	0.11897345	19	0.516949635	0.00471771
FANCD2	chr3	0.00038781	0.12395813	8	0.520584218	0.00790724
ZNF471	chr19	0.00044648	0.12447833	22	0.520584218	0.00800901
CNTN4	chr3	0.00049386	0.12103067	22	0.520584218	0.00839564
KIR3DL3	chr19	0.0042929	0.12953561	28	0.526289354	0.03747586
CTNND2	chr5	0.00032283	0.13173874	6	0.528591446	0.00744823
CNTN6	chr3	0.00148207	0.1359894	27	0.532419115	0.01824453
SSTR1	chr14	0.00257318	0.13529664	31	0.532419115	0.02681089

DCHS2	chr4	0.0014337	0.14360795	12	0.536048728	0.01823688
FSHR	chr2	0.00423293	0.1438578	20	0.536048728	0.03745849
IFNA2	chr9	0.00141094	0.14809973	23	0.537485527	0.01823688
FHIT	chr3	0.0012614	0.15680903	9	0.553798892	0.01764958
DEFA1	chr8	0.00153238	0.15688111	18	0.553798892	0.01833179
FGF14	chr13	7.79E-07	0.17677207	16	0.610667167	8.38E-05
IL17RD	chr3	0.00371326	0.1830702	5	0.622438694	0.03426812
CHP2	chr16	0.00641107	0.18960549	12	0.625728017	0.0464844
REG1A	chr2	0.00497341	0.1947963	23	0.626061747	0.04119007
FGA	chr4	0.0012841	0.20233997	12	0.640743241	0.01764958
FGF9	chr13	4.78E-06	0.21096731	9	0.650090211	0.00034277
PTPN21	chr14	0.00022182	0.22797658	23	0.66583076	0.00551139
SLC10A2	chr13	0.00101645	0.22819505	28	0.66583076	0.0149234
FAM19A1	chr3	9.84E-05	0.246153	26	0.687426094	0.00397137
SRGAP3	chr3	0.00017448	0.25481058	9	0.687426094	0.00515291
TSHR	chr14	0.00293901	0.25751875	17	0.687426094	0.02920925
SERPINB4	chrNA	0.00654811	0.27362155	21	0.704221208	0.0464844
RXFP2	chr13	0.00176575	0.27477855	21	0.704392626	0.01966686
ROBO2	chr3	5.22E-05	0.31573061	15	0.763902522	0.00259566
GLMN	chr1	0.00036543	0.31101145	7	0.763902522	0.00790724
ZBTB16	chr11	0.00540913	0.31359359	8	0.763902522	0.04313949
KIR2DL4	chrNA	0.00537859	0.31359456	21	0.763902522	0.04313949
IGFALS	chr16	0.00109405	0.34549007	8	0.799951915	0.01570571
CCK	chr3	0.00272149	0.33939734	21	0.799951915	0.02747003
CSMD3	chr8	0.00633737	0.36412022	13	0.813915784	0.0464844
TRAF7	chr16	0.00731847	0.3628936	8	0.813915784	0.04999367
OXTR	chr3	0.00630022	0.50858989	30	0.933378029	0.0464844
LEPR	chr1	0.00101565	0.51531361	7	0.936961581	0.0149234
TNFSF11	chr13	0.00061	0.56976994	6	0.952836439	0.0101041
FRMD7	chr23	0.00448599	0.89493291	5	1	0.03863934