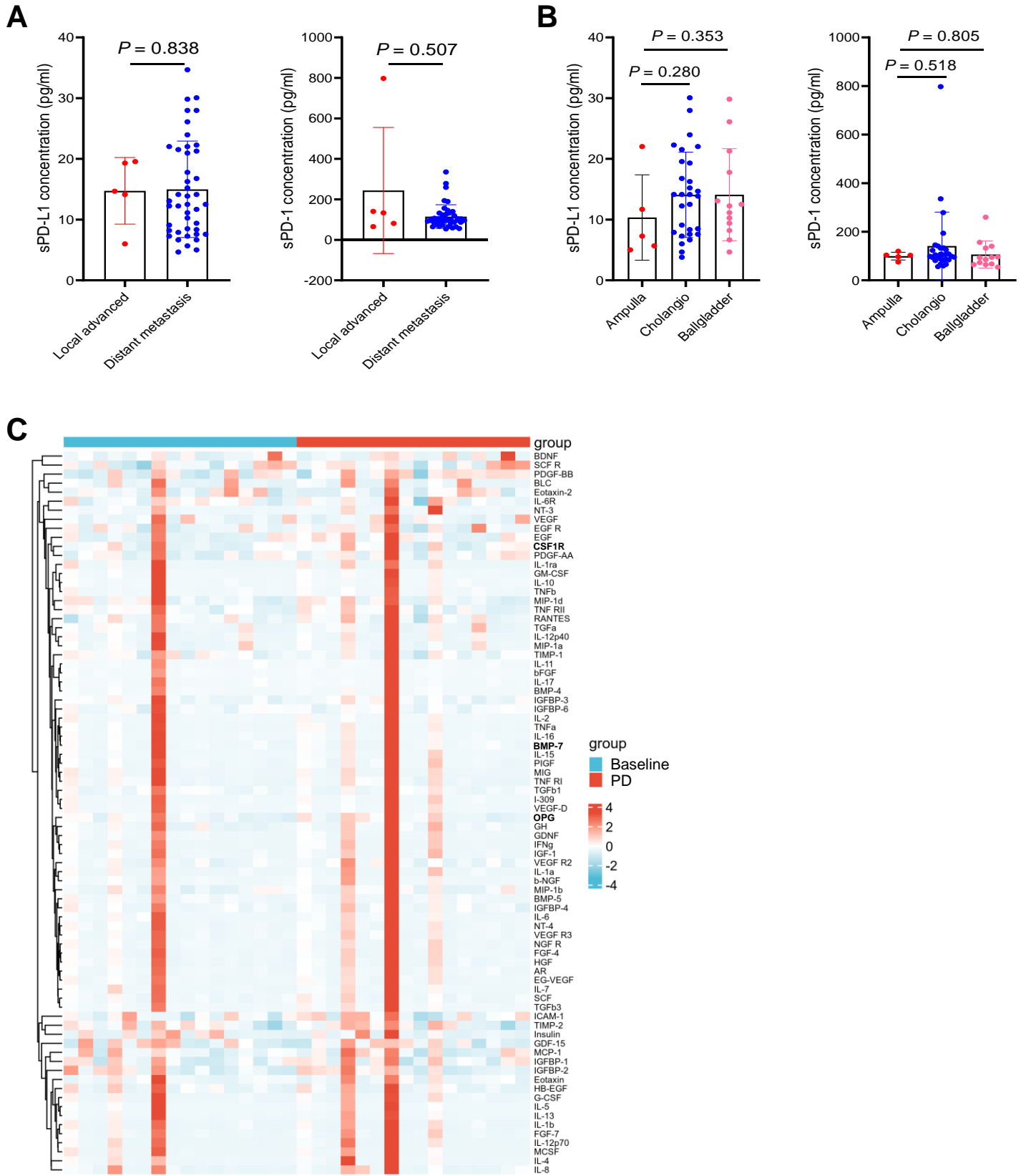
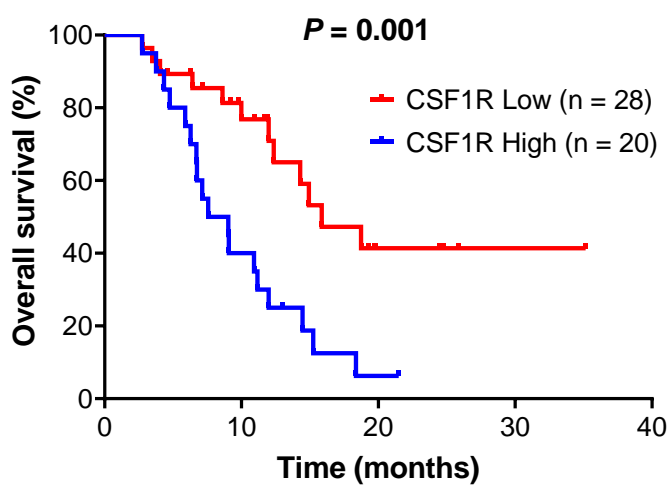
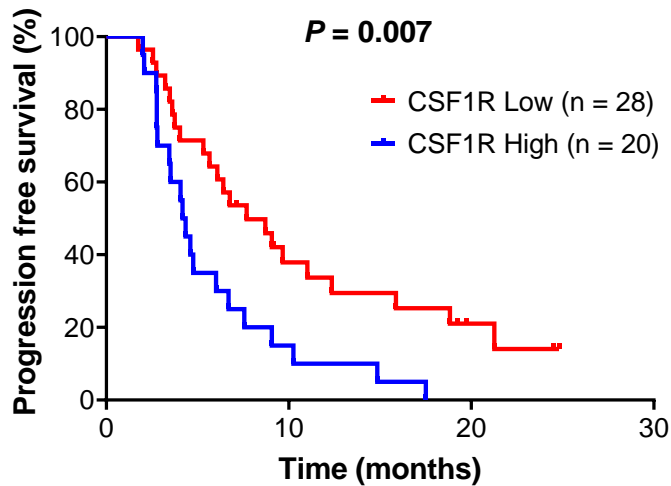


Supplementary Figure 1

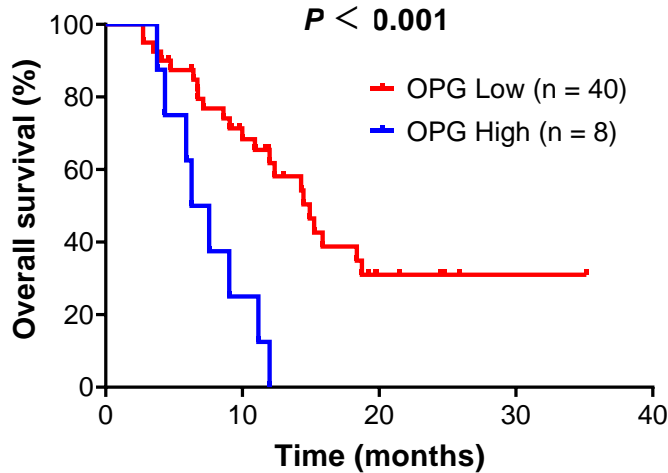
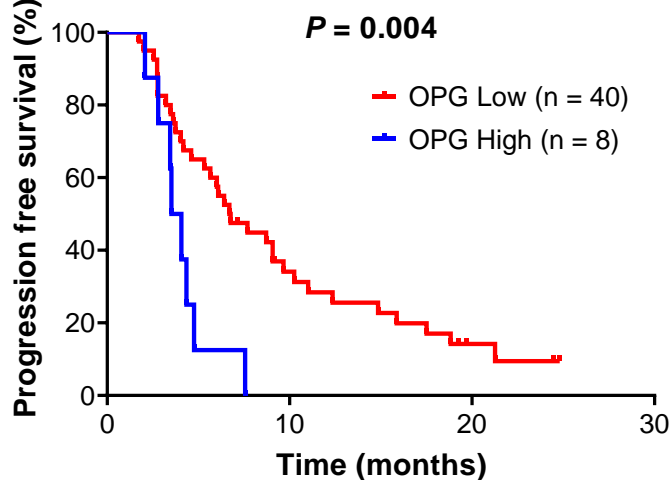


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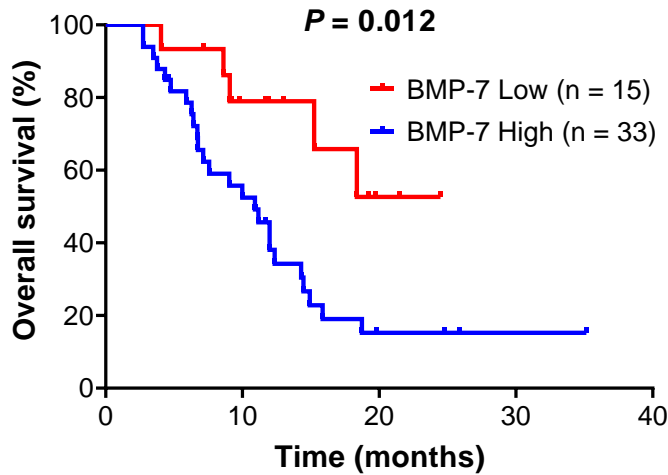
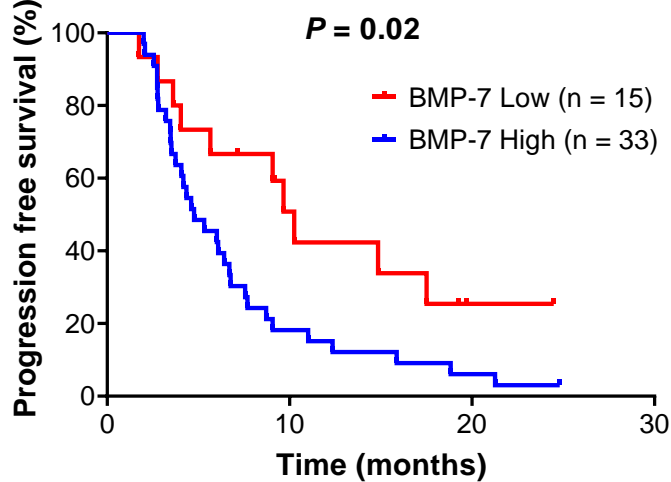
A



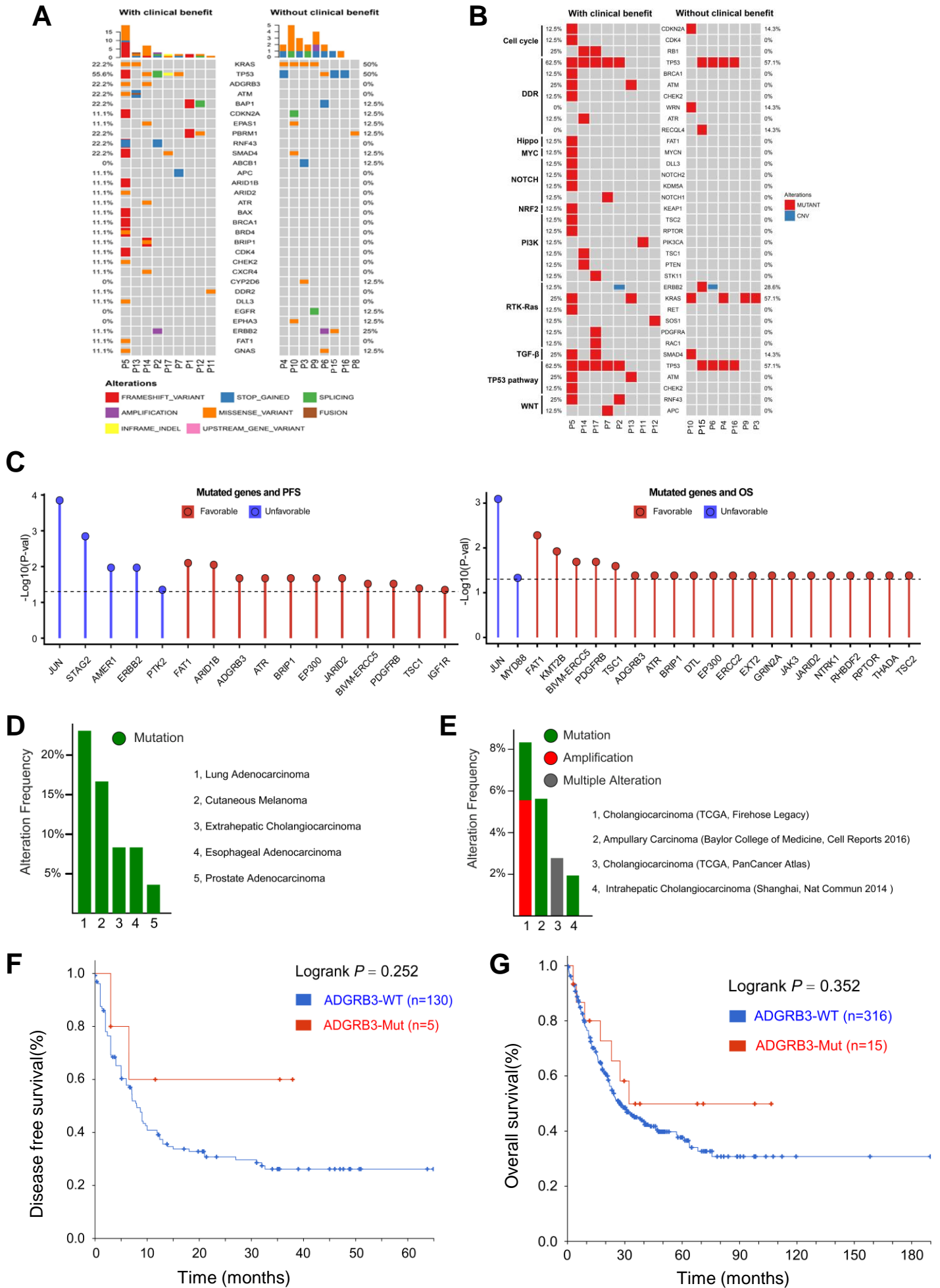
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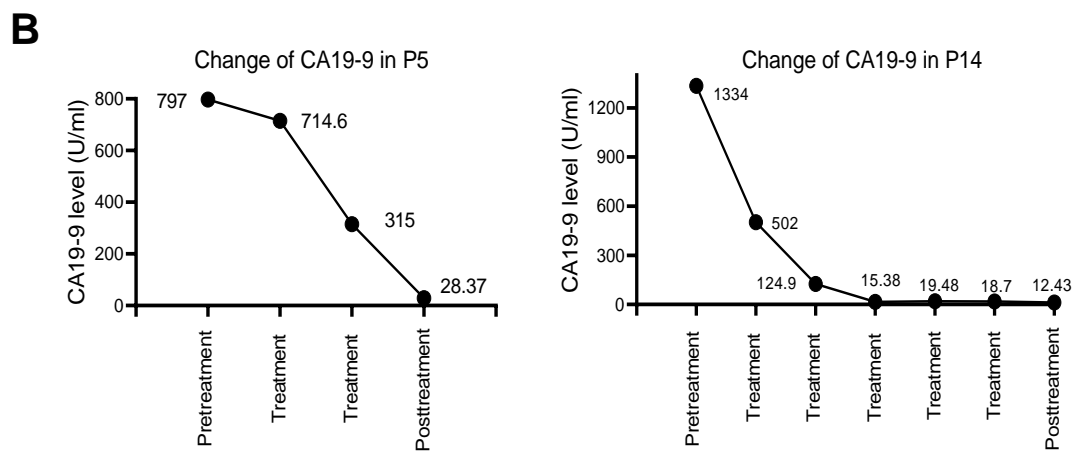
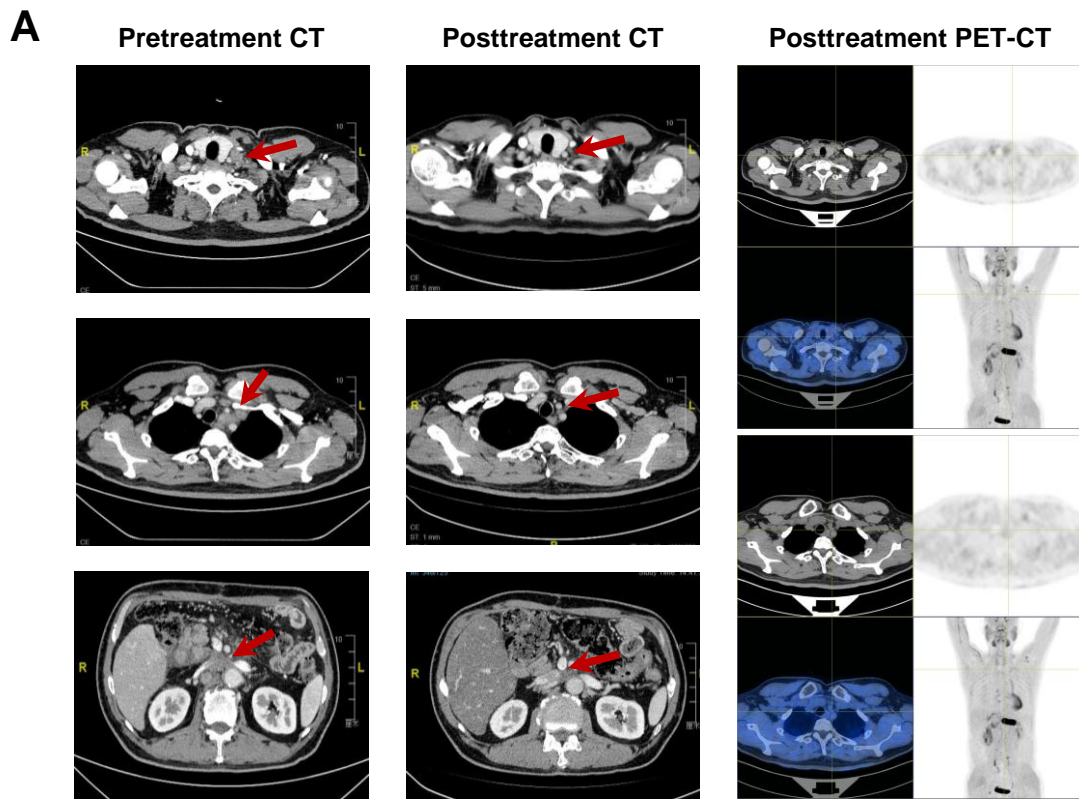
C



Supplementary Figure 3



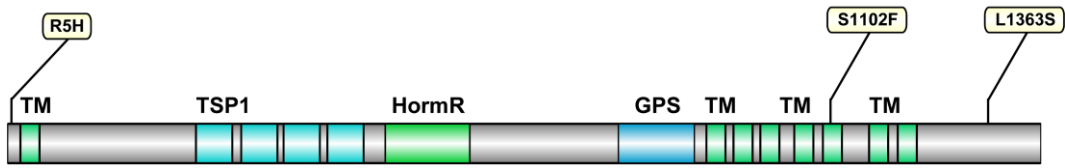
Supplementary Figure 4



Supplementary Figure 5

A

ADGRB3

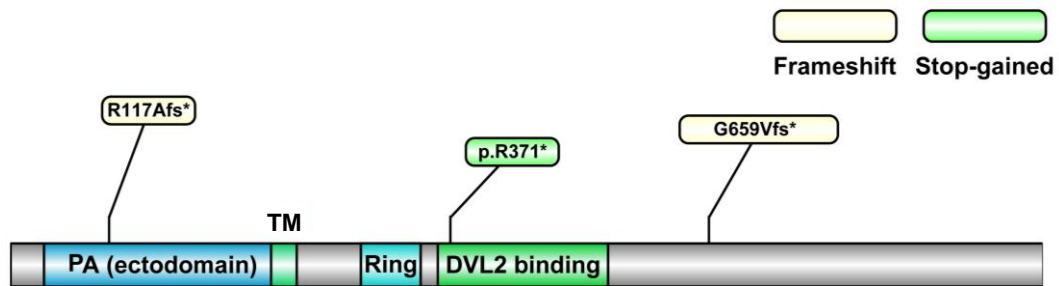


B

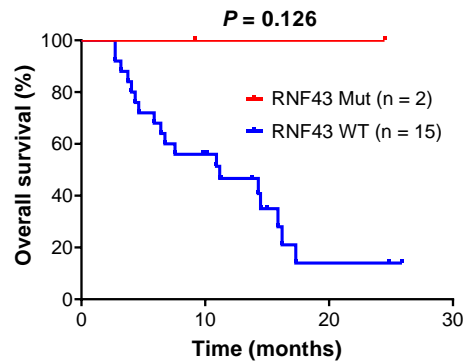
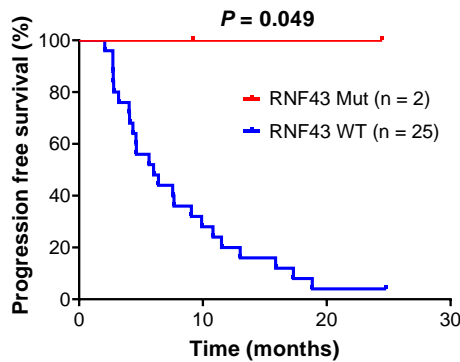
ID	Gene	Amino acid change	ExonicFunc	OncoKB	Polyphen2
P2	RNF43	p.R371*	stop_gained	Damaging	
P5	RNF43	p.R117Afs*41	frameshift_variant	Damaging	
P5	RNF43	p.G659Vfs*41	frameshift_variant	Damaging	
P5	RNF43	p.R371*	stop_gained	Damaging	
P5	ADGRB3	p.L1363S	missense_variant		Damaging
P5	ADGRB3	p.R5H	missense_variant		Damaging
P14	ADGRB3	p.S1102F	missense_variant		Damaging

C

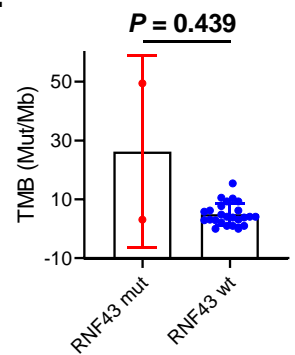
RNF43



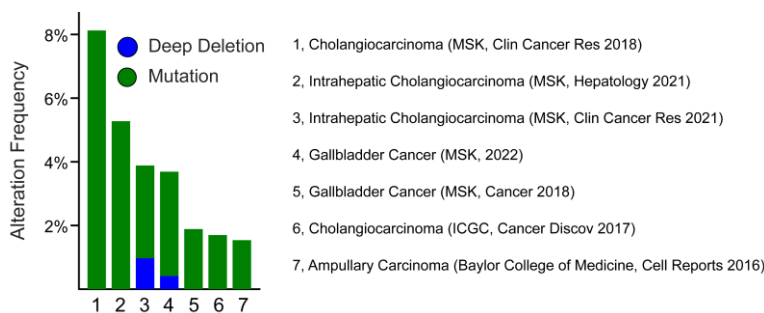
D



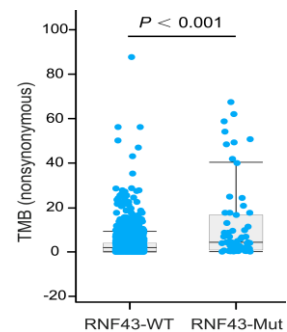
E



F



G



1 **Supplementary Figure legends**

2 **Figure S1. Associations of sPD-L1 and sPD-1 with tumor stage and**
3 **location.** Associations of sPD-L1 and sPD-1 with disease stage (A) and
4 tumor location (B). (C) Relative levels of detected cytokines in paired
5 blood samples collected at baseline and the disease progression time point.
6 ABC, advanced biliary tract cancer; sPD-L1, soluble programmed death
7 ligand 1; sPD-1, soluble programmed death 1.

8

9 **Figure S2. Survival prediction of CSF1R, OPG and BMP-7.** PFS and
10 OS in ABC patients receiving chemotherapy with durvalumab according
11 to relative levels of CSF1R (A), OPG (B) and BMP-7 (C).

12 PFS, progression free survival; OS, overall survival; ABC, advanced
13 biliary tract cancer; CSF1R, colony-stimulating factor 1 receptor; OPG,
14 osteoprotegerin; BMP-7; bone morphogenetic protein 7.

15

16 **Figure S3. Pathway analysis and ADGRB3 mutations in the cBioPortal**
17 **database.** (A) Waterfall plots showing the frequency and types of top
18 mutated genes found in 17 ABC patients underwent target sequencing of
19 437 cancer related genes who did or did not benefit from durvalumab. (B)
20 Pathway enrichment ABC patients who did or did not benefit from
21 durvalumab. (C) Mutated genes associated with PFS and OS in our cohort.
22 Mutation frequency of ADGRB3 in solid tumors (D) and

23 cholangiocarcinoma (E) from the cBioPortal database. Disease free
24 survival (DFS) (F) and OS (G) in ABC patients with or without ADGRB3
25 mutations in the cBioPortal database.

26 ABC, advanced biliary tract cancer; ADGRB3, adhesion G protein coupled
27 receptor B3; PFS, progression free survival; OS, overall survival; DFS,
28 disease free survival.

29

30 **Figure S4. Clinical response of patients P5 and P14 to durvalumab.** (A)

31 Pre- and posttreatment CT scans as well as PET/CT images of patient P14.

32 (B) Pre- and posttreatment CA19-9 levels in patients P5 and P14.

33

34 **Figure S5. Clinical associations of ADGRB3 and RNF43 mutations.** (A)

35 Schematic illustration of ADGRB3 mutations detected in our samples. (B)

36 Summary of ADGRB3 and RNF43 mutations. (C) Schematic illustration

37 of RNF43 mutations detected in our samples. (D) PFS and OS of RNF43

38 Mut and WT patients treated with chemotherapy plus durvalumab. (E)

39 TMB degree of RNF43-mutated and WT patients. (F) Mutation frequency

40 of RNF43 in cholangiocarcinoma from the cBioPortal database. (G) TMB

41 in cholangiocarcinoma patients with or without the RNF43 mutation from

42 the cBioPortal database.

43 ADGRB3, adhesion G protein coupled receptor B3; RNF43, Ring Finger

44 Protein 43; TM, transmembrane region; TSP1, thrombospondin type 1

45 repeats; HormR, domain present in hormone receptors; GPS, G-protein-
46 coupled receptor proteolytic site domain; Mut, mutation; WT, wild type.

Supplementary Table 1. Uni and multivariate cox analysis of different clinical pathological indices with PFS in patients receiving durvalumab

Characteristics	Total (N)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	<i>P</i> value	Hazard ratio (95% CI)	<i>P</i> value
Age	93	0.10 (0.97 - 1.02)	0.626		
Sex	93				
Male	51	Reference			
Female	42	1.24 (0.80 - 1.92)	0.344		
Differentiation	93				
Poor	52	Reference			
High or intermediate	41	0.68 (0.44 - 1.06)	0.087		
Disease stage	93				
Locally advanced	11	Reference			
Distant metastasis	82	1.92 (0.88 - 4.18)	0.099		
Primary site	93				

Characteristics	Total (N)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Intrahepatic	43	Reference			
Gallbladder	27	0.96 (0.57 - 1.61)	0.868		
Extrahepatic	14	1.18 (0.62 - 2.23)	0.614		
Ampulla	9	0.92 (0.40 - 2.11)	0.846		
Liver metastasis	93				
Present	59	Reference			
Absent	34	0.68 (0.42 - 1.08)	0.102		
Prior surgery of primary tumor	93				
No surgery	41	Reference			
Radical surgery	43	0.77 (0.48 - 1.22)	0.259		
Palliative surgery	9	0.51 (0.23 - 1.16)	0.108		
ECOG	93				
1	81	Reference		Reference	

Characteristics	Total (N)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	<i>P</i> value	Hazard ratio (95% CI)	<i>P</i> value
0	12	0.52 (0.27 - 1.02)	0.056	0.93 (0.42 - 2.04)	0.857
WBC	93	1.05 (0.97 - 1.12)	0.240		
NLR	93	1.09 (1.01 - 1.16)	0.018	1.04 (0.94 - 1.15)	0.435
Basophil	93	0.00 (0.00 - 0.62)	0.040	0.00 (0.00 - 0.13)	0.020
PLT	93	1.00 (1.00 - 1.00)	0.777		
ALP	91	1.00 (1.00 - 1.00)	< 0.001	1.00 (1.00 - 1.01)	0.243
GGT	91	1.00 (1.00 - 1.00)	0.008	1.00 (1.00 - 1.00)	0.312
LDH	93	1.01 (1.00 - 1.01)	0.003	1.00 (1.00 - 1.01)	0.204
ALB	93	0.95 (0.91 - 1.00)	0.039	0.99 (0.92 - 1.06)	0.721
CRP	93	1.01 (1.00 - 1.02)	0.003	1.00 (0.99 - 1.01)	0.649
Fbg	81	1.14 (1.02 - 1.27)	0.022	1.29 (1.07 - 1.55)	0.008
CA19-9	89	1.00 (1.00 - 1.00)	0.020	1.00 (1.00 - 1.00)	0.028

The bold *P* values indicate statistically significant.

Supplementary Table 2. Uni and multivariate cox analysis of different clinical pathological indices with OS in patients receiving durvalumab

Characteristics	Total (N)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	<i>P</i> value	Hazard ratio (95% CI)	<i>P</i> value
Age	93	1.03 (1.00 - 1.06)	0.052		
Sex	93				
Male	51	Reference			
Female	42	0.90 (0.53 - 1.53)	0.690		
Differentiation	93				
High or intermediate	41	Reference		Reference	
Poor	52	0.58 (0.34 - 1.01)	0.052	0.56 (0.26 - 1.22)	0.145
Disease stage	93				
Locally advanced	11	Reference			
Distant metastasis	82	1.14 (0.49 - 2.67)	0.763		
Primary site	93				

Characteristics	Total (N)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	P value	Hazard ratio (95% CI)	P value
Intrahepatic	43	Reference			
Gallbladder	27	0.68 (0.35 - 1.30)	0.241		
Extrahepatic	14	0.90 (0.41 - 1.97)	0.790		
Ampulla	9	0.71 (0.27 - 1.85)	0.483		
Liver metastasis	93				
Present	59	Reference		Reference	
Absent	34	0.55 (0.30 – 1.00)	0.048	0.65 (0.29 - 1.47)	0.305
Prior surgery of primary tumor	93				
No surgery	41	Reference		Reference	
Radical surgery	43	0.48 (0.27 - 0.85)	0.012	0.85 (0.35 - 2.09)	0.730
Palliative surgery	9	0.41 (0.14 - 1.17)	0.095	0.60 (0.16 - 2.30)	0.456
ECOG	93				
1	81	Reference			

Characteristics	Total (N)	Univariate analysis		Multivariate analysis	
		Hazard ratio (95% CI)	<i>P</i> value	Hazard ratio (95% CI)	<i>P</i> value
0	12	0.51 (0.22 - 1.20)	0.124		
WBC	93	1.08 (0.99 - 1.17)	0.098		
NLR	93	1.11 (1.02 - 1.21)	0.009	1.17 (1.01 - 1.35)	0.040
Basophil	93	0.05 (0.00 - 136)	0.447		
PLT	93	1.00 (1.00 - 1.00)	0.890		
ALP	91	1.00 (1.00 - 1.00)	0.002	1.00 (1.00 - 1.00)	0.749
GGT	91	1.00 (1.00 - 1.00)	0.006	1.00 (1.00 - 1.00)	0.902
LDH	93	1.00 (1.00 - 1.01)	0.045	1.00 (1.00 - 1.01)	0.943
ALB	93	0.93 (0.88 - 0.99)	0.014	0.95 (0.88 - 1.03)	0.219
CRP	93	1.01 (1.00 - 1.02)	0.005	1.00 (0.98 - 1.01)	0.557
Fbg	81	1.18 (1.02 - 1.37)	0.023	1.08 (0.86 - 1.36)	0.489
CA199	89	1.00 (1.00 - 1.00)	0.433		

The bold *P* values indicate statistically significant.