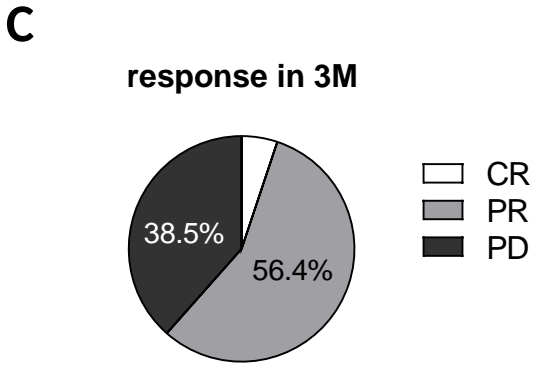
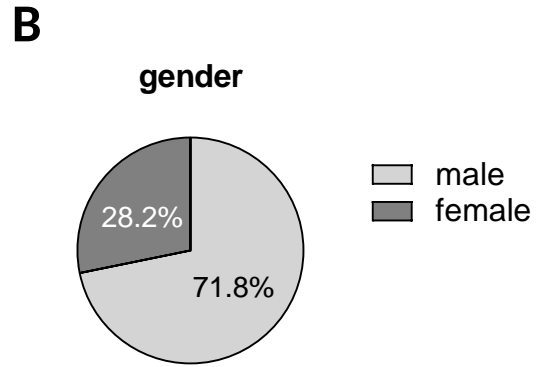
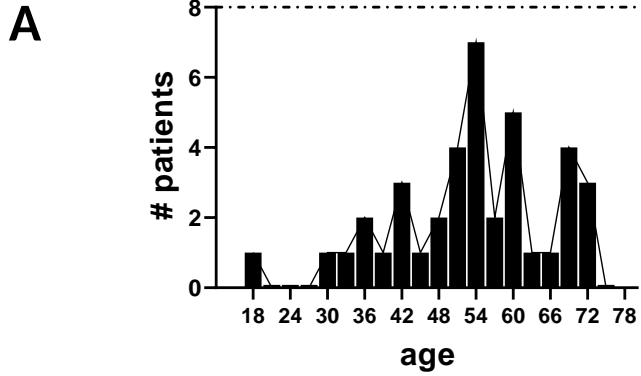
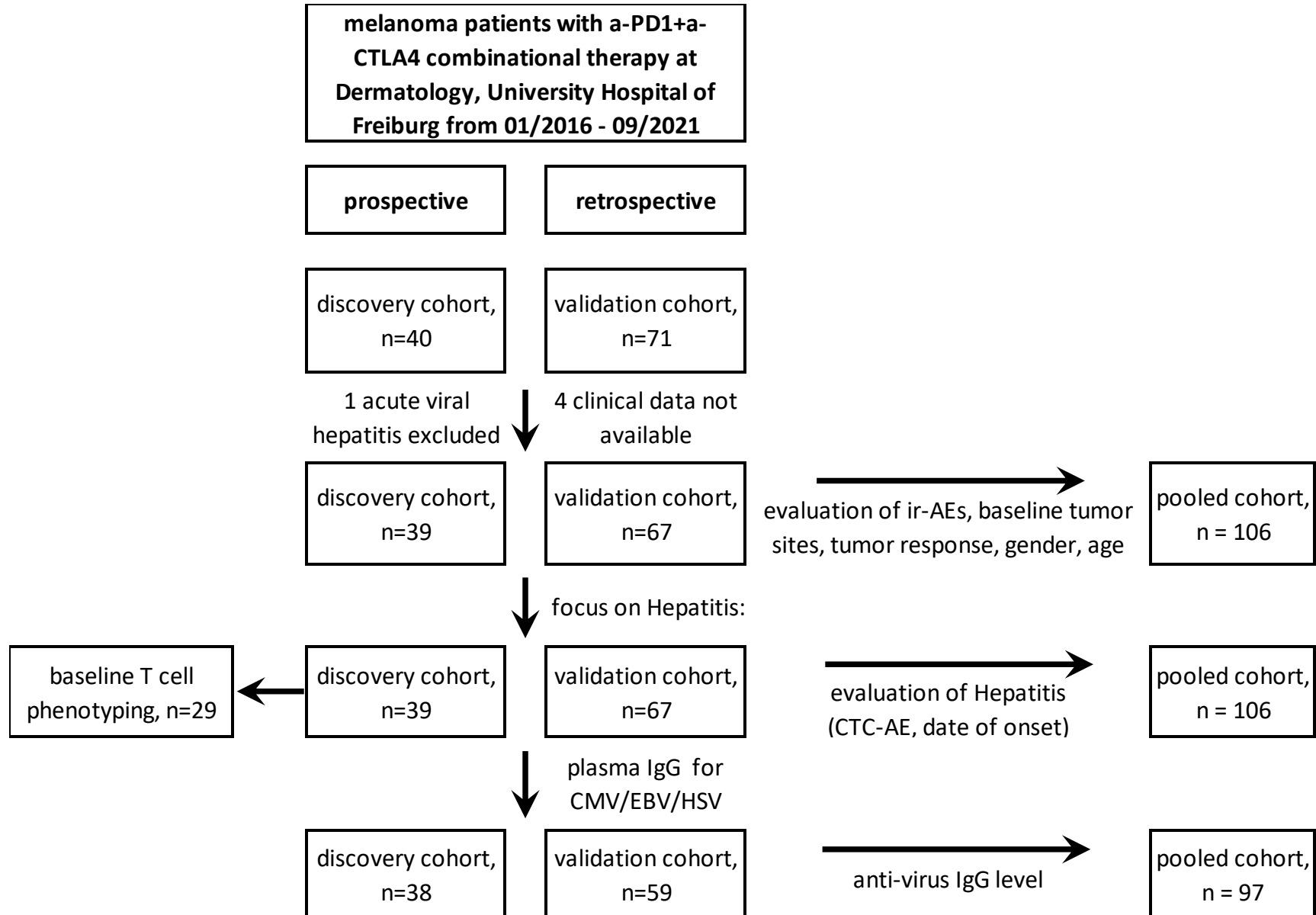


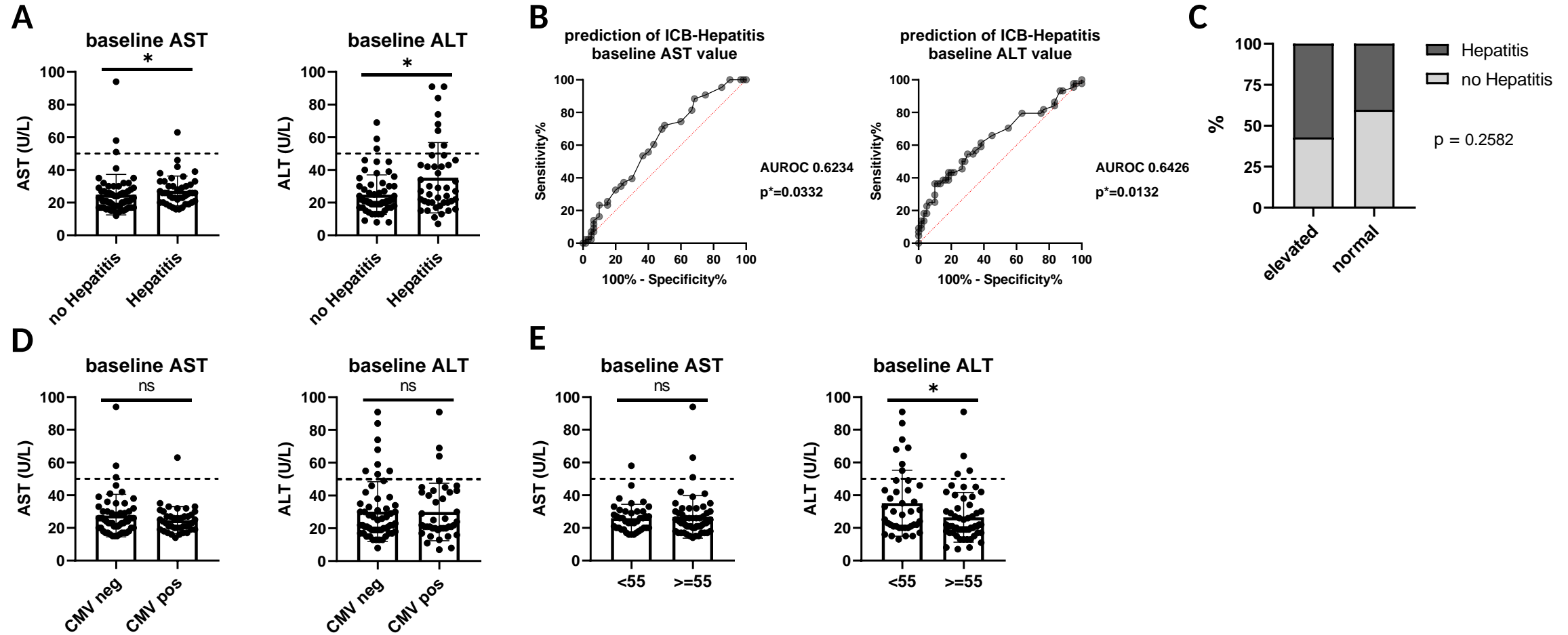
s.Fig.1 Characteristics of discovery cohort.



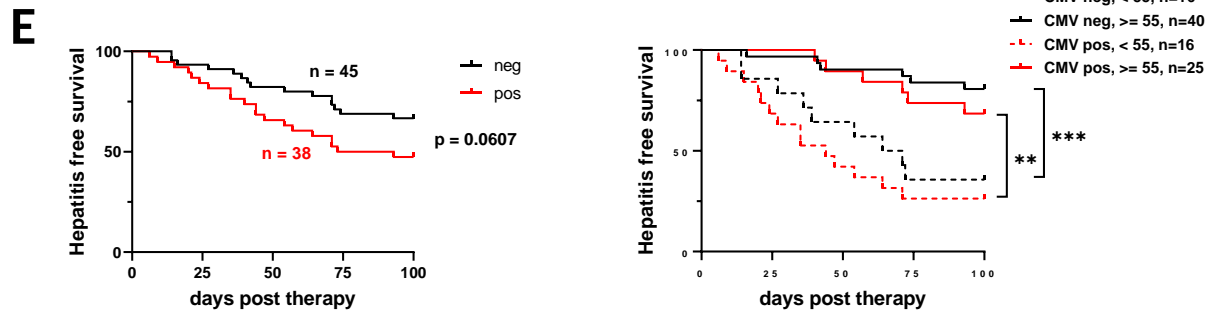
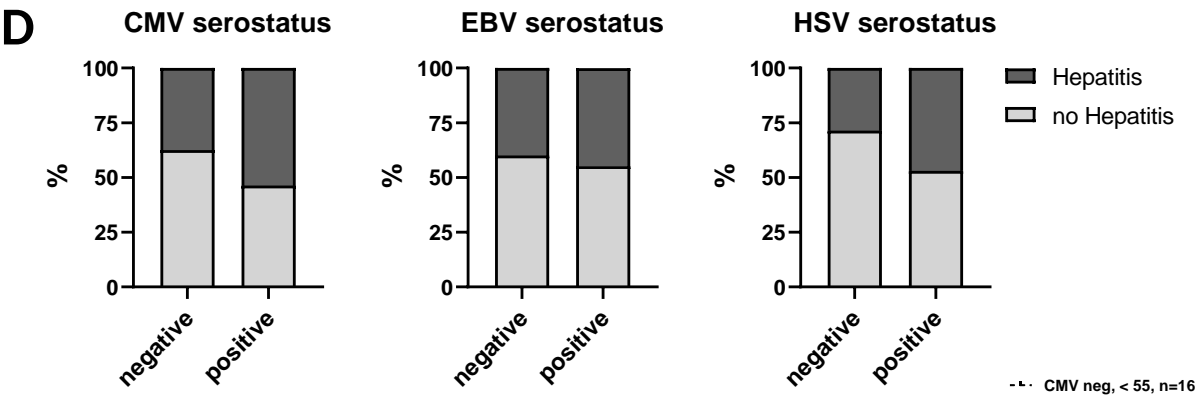
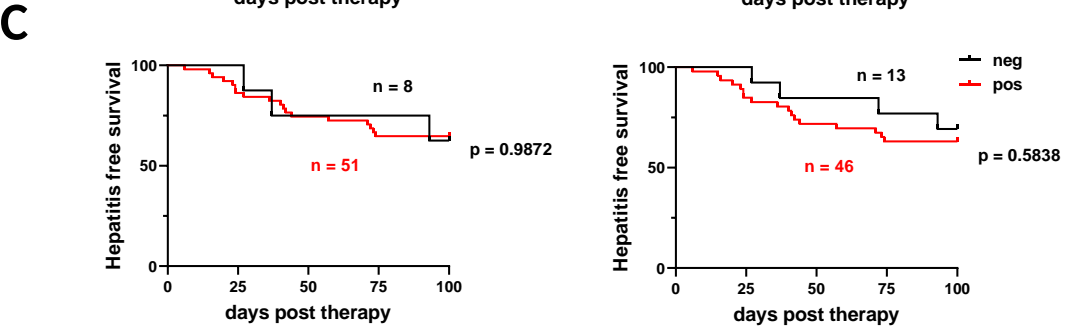
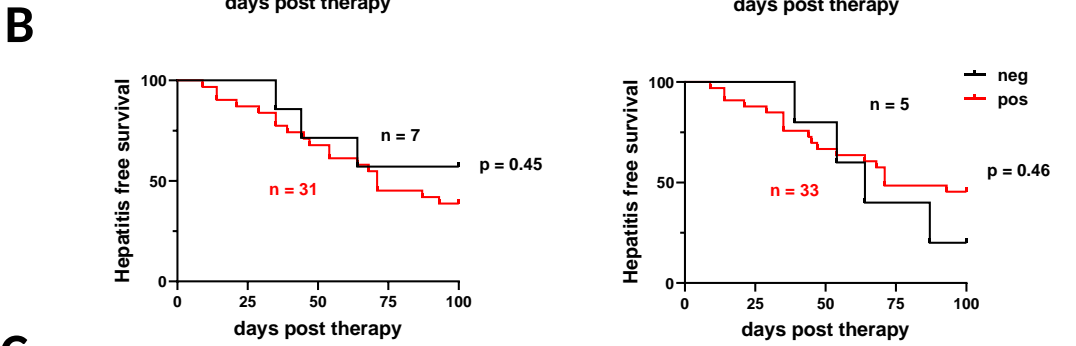
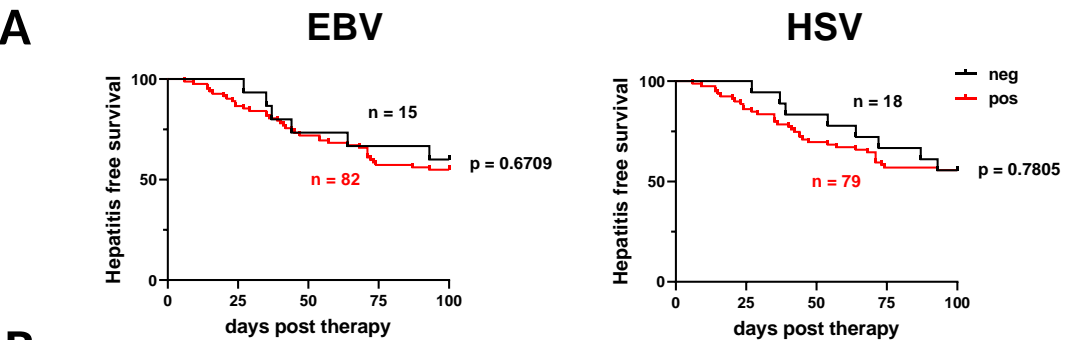
s.Fig.2 Workflow of patient selection



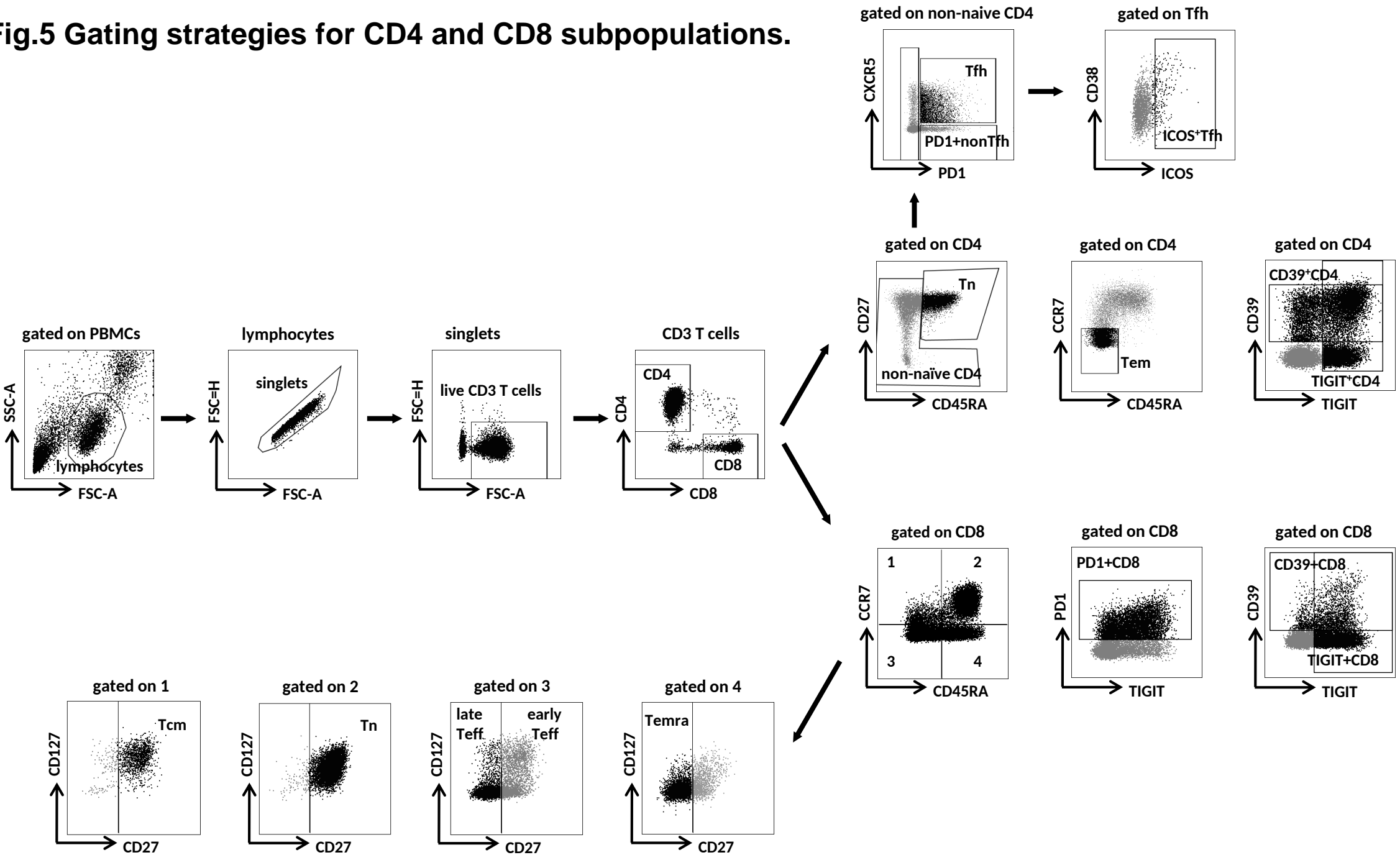
s.Fig.3 Baseline AST and ALT values are associated with therapy-induced hepatitis.



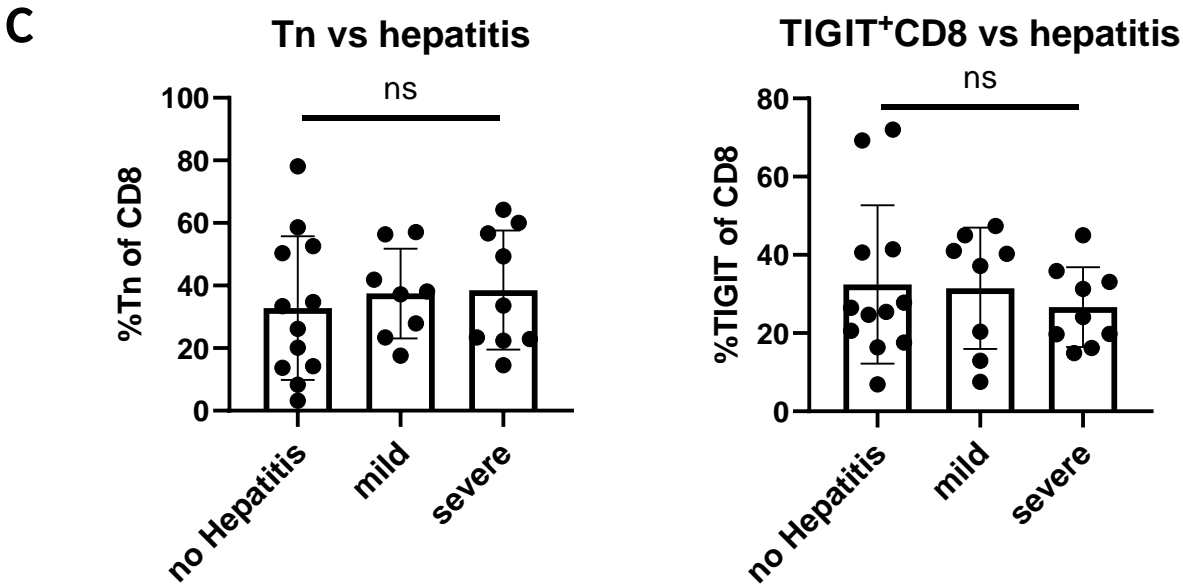
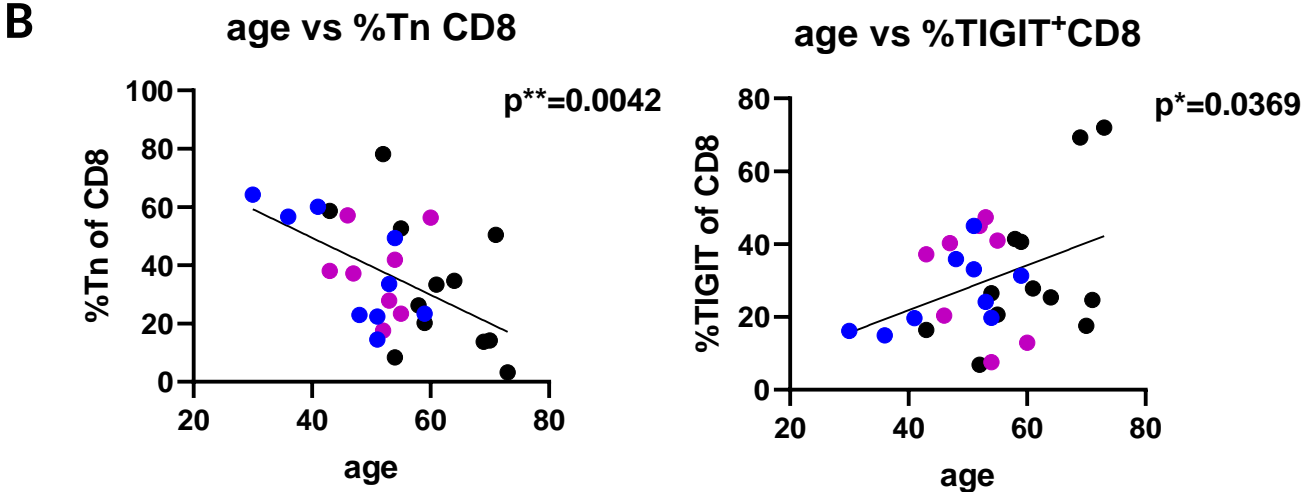
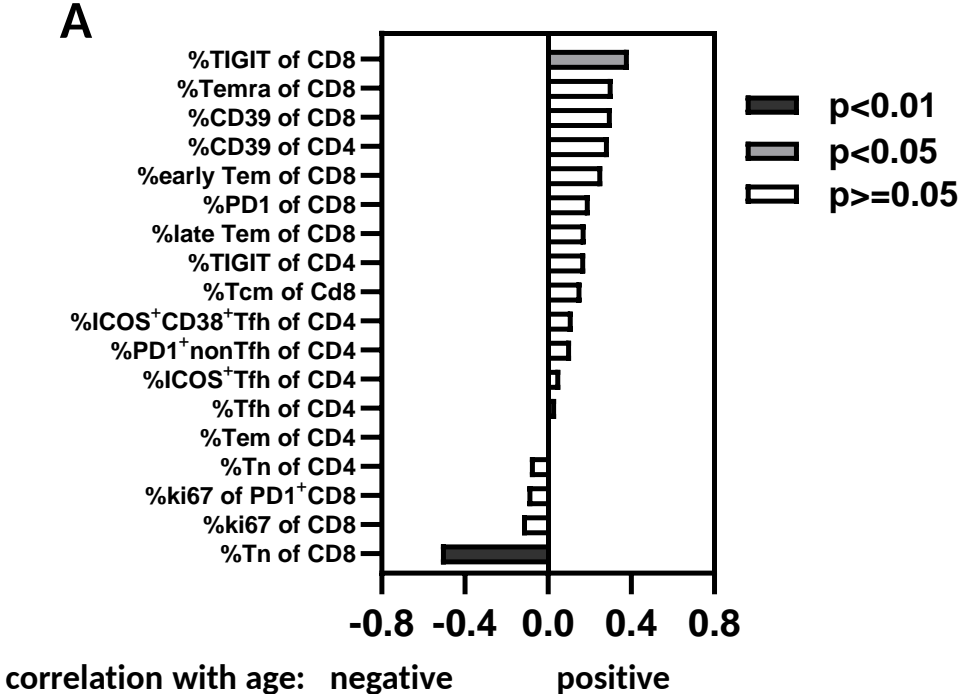
s.Fig.4 EBV/HSV/CMV IgG serostatus does not correlate with Immune-checkpoint hepatitis.



s.Fig.5 Gating strategies for CD4 and CD8 subpopulations.

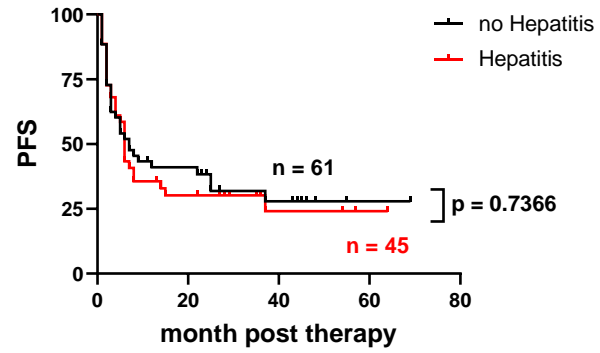


s.Fig.6 Age-associated T cell populations are not related to incidence of Hepatitis

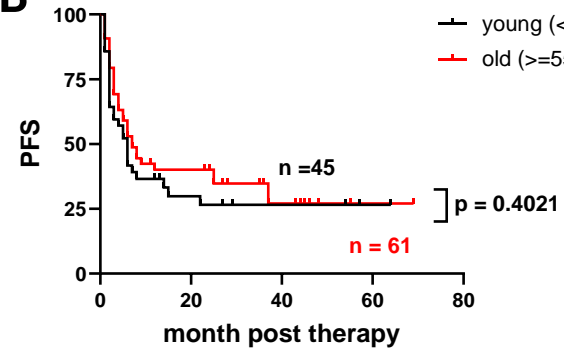


s.Fig.7 Tumor progression-free survival analysis according to ICB-hepatitis, age and irAE

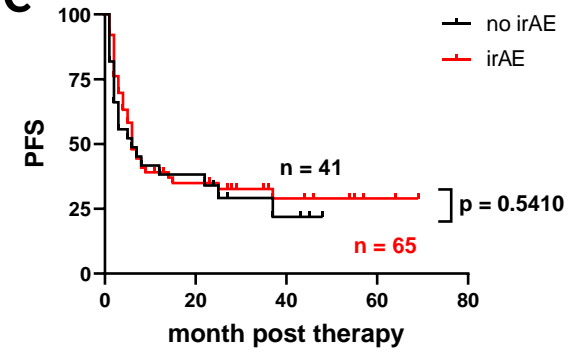
A



B



C



Supplemental Table 1:

	hepatitis	no hepatitis	total
responders(CR+PR+SD)	16	9	25
non-responders(PD)	8	6	14

p=0.7397

	hepatitis	no hepatitis	total
male	16	12	28
female	7	4	11

p>0.99

Contingency table comparing distribution of tumor response and gender in patients with/without hepatitis in discovery cohort.

Supplemental Table 2:

	discovery cohort(n=39)	validation cohort(n=67)	test performed	p value
age				
median age	54	60	Mann-Whitney Test (two-tailed)	0.0305
min. age	19	25		
max. age	73	80		
gender				
male	28	46	Chi Square Test	0.7343
female	11	21		
tumor response in 3 months §				
CR	2	7	Chi Square Test	<0.0001
PR	22	9		
SD	0	14		
PD	15	26		
NE	0	11		
no. of ir-AEs				
0	8	29	Chi Square Test	0.0016
1	10	18		
2	6	15		
3	9	4		
>= 4	6	1		
incidence of Hepatitis				
no Hepatitis	16	45	Chi Square Test	0.0086
Hepatitis	23	22		
severity of Hepatitis				
CTC-AE I	1	1	Chi Square Test	0.8369
CTC-AE II	8	5		
CTC-AE III	10	12		
CTC-AE IV	4	4		

Clinical information of patients included in the discovery and validation cohort.

§ CR: complete response, PR: partial response, PD: progression disease, SD: stable disease,

NE: not evaluable. Comparison excluded patients with NE response.

Supplemental Table 3

	No. of patients evaluated	no Hepatitis, n=61	Hepatitis, n=45	test performed	p value
age					
median age	n=106	64	52	Mann-Whitney Test (two-tailed)	<0.0001
min. age		25	19		
max. age		79	80		
gender					
male	n=106	46	28	Chi Square Test	0.1438
female		15	17		
tumor response in 3 months §					
CR	n=94	4	4	Chi Square Test	0.1482
PR		13	18		
SD or MR		11	3		
PD		23	18		
NE		10	2		
CMV IgG status					
positive	n=97	24	22	Chi Square Test	0.5104
negative		30	21		
AST					
median(95% CI)	n=101	21.5(20-26)	26(23-29)	Mann-Whitney Test (two-tailed)	0.0326
ALT					
median(95% CI)	n=102	21(19-24)	28(22-42)	Mann-Whitney Test (two-tailed)	0.0128
liver metastasis					
no	n=106	46	31	Chi Square Test	0.4567
yes		15	14		
no. of non-Hepatitis irAE *					
0	n=106	41	15	Chi Square Test	0.0003
1		17	15		
2		3	11		
3		0	4		
4		0	0		
BRAF §					
other mutations	n=101	1	4	Chi Square Test	0.1784
V600 mutation		24	16		
wt		35	21		
unknown		1	4		
NRAS §					
other mutations	n=91	2	1	Chi Square Test	0.7508
Q61 mutation		15	14		
wt		35	24		
unknown		9	6		
stage					
III	n=106	3	2	Fisher's Exact Test (two-tailed)	>0.9999
IV		58	43		
LDH level					
normal	n=93	26	23	Chi Square Test	0.5587
elevated		26	18		
HBsAg					
negative	n=99	55	43	Fisher's Exact Test (two-tailed)	>0.9999
positive		1	0		
anti-HBc antibody					
negative	n=99	53	39	Fisher's Exact Test (two-tailed)	0.4638
positive		3	4		
anti-HBs antibody					
negative	n=99	44	26	Chi Square Test	0.0497
positive		12	17		
anti-HCV antibody					
negative	n=98	55	43	Fisher's Exact Test (two-tailed)	>0.9999
positive		0	0		
anti-HIV antibody					
negative	n=98	55	43	Fisher's Exact Test (two-tailed)	>0.9999
positive		0	0		

f patients who developed hepatitis or not in pooled cohort

* only included skin abnormality, thyroiditis, enteritis and hypophysitis

§ Comparison excluded patients with NE response or unknown status