

100nM		Tumor killing (%)	
Class	Small molecule	Small molecule alone	CART19 + Small molecule
BCL-2	TW-37	45.22508307	17.073373
	AT101	-0.70466302	20.1618895
	ABT-199 (GDC-0199)	47.83647713	88.2474329
	ABT-263 (Navitoclax)	-4.53394741	31.0351855
	BAM7	-4.13026466	2.24513259
	HA14-1	-0.931592024	27.847702
Caspase	Obatoclax Mesylate (GX15-070)	33.09065329	79.5794198
	Apoptosis Activator 2	3.616110819	14.3620513
Ferroptosis	PAC-1	-2.249832868	16.5878746
	Erasin	8.218298764	15.5639055
IAP	Embelin	-4.328684995	15.5639055
	AT-406	-22.89923183	6.10713552
	GDC-0152	3.172515933	20.8808005
	Birinapant	5.145315812	92.4955436
	Tenovin-1	1.848573355	15.7755985
p53	JNJ-26854165 (Serdemelan)	-4.874911089	12.9877175
	NSC319726	90.56641023	140.729806

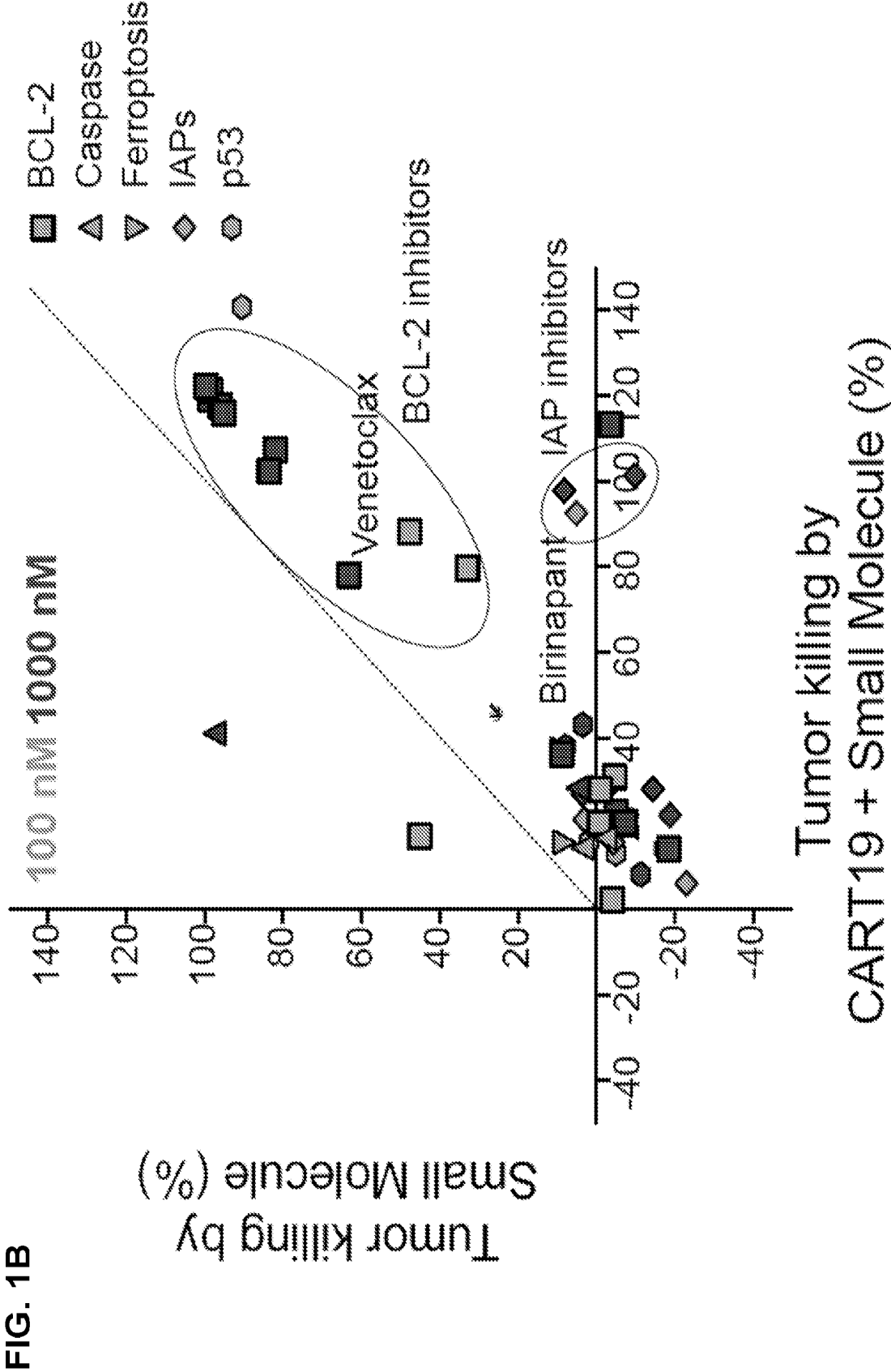
FIG. 1A – 1 of 3

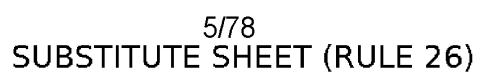
1000nM		Tumor killing (%)	
Class	Small molecule	Small molecule alone	CART19 + Small molecule
Bcl-2	HA14-1	8.911750928	36.2545263
	A-1331852	98.80105475	119.199146
	Sabutoclax	98.49093496	121.083158
	A-1155463	96.00861349	117.597919
	BDA-366	99.65439535	122.247352
	TW-37	82.05179899	107.400555
	ABT-199 (GDC-0199)	63.25122471	78.1571199
	ABT-263 (Navitoclax)	83.49682989	102.357687
	AT101	-3.509081702	113.391762
	UMI-77	-4.966632877	22.5090288
	BAM7	-7.240914979	20.1408332
	BH3I-1	-18.39014603	14.0782504
	Obatoclax Mesylate (GX15-070)	95.14143634	115.874653
	PAC-1	4.884356941	28.3191352
Caspase	Apoptosis Activator 2	97.54172917	41.1037826
Ferroptosis	Erasin	8.918580125	37.3544141
	RSL3	99.56115898	122.18166

FIG. 1A – 2 of 3

IAP	Birinapant	8.308491491	97.835599
	LCL161	-18.76710535	22.0336836
	Embelin	3.663879348	26.863462
	GDC-0152	-4.222190191	29.5731296
	BV-6	-9.724756434	101.239042
	AT-406	-14.3914207	28.0681571
	NSC59984	3.559018978	43.0738772
P53	NSC319726	98.81864855	121.606814
	NSC348884	-4.735738019	21.6044978
	PRIMA-1	-11.2348987	8.11221215
	APR-246 (PRIMA-1MET)	-17.20146711	14.2040348
	Tenovin-1	7.944350986	37.9477324
	JNJ-26854165 (Serdemetan)	1.40135301	28.3119644

FIG. 1A – 3 of 3





Venetoclax enhances the cytotoxicity of CART19 against non-Hodgkin lymphoma *in vitro*

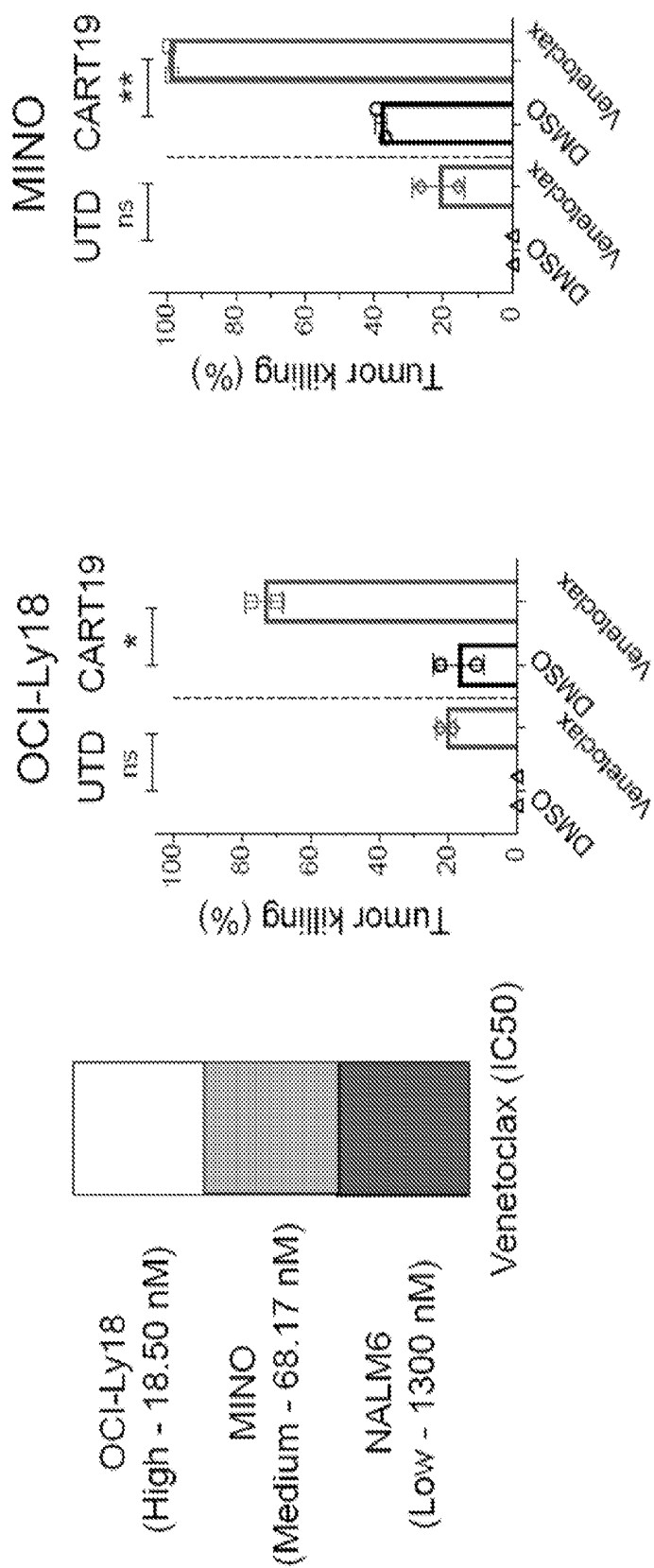


FIG. 1D – 1 of 2

Venetoclax enhances the cytotoxicity of CART19 against non-Hodgkin lymphoma *in vitro*

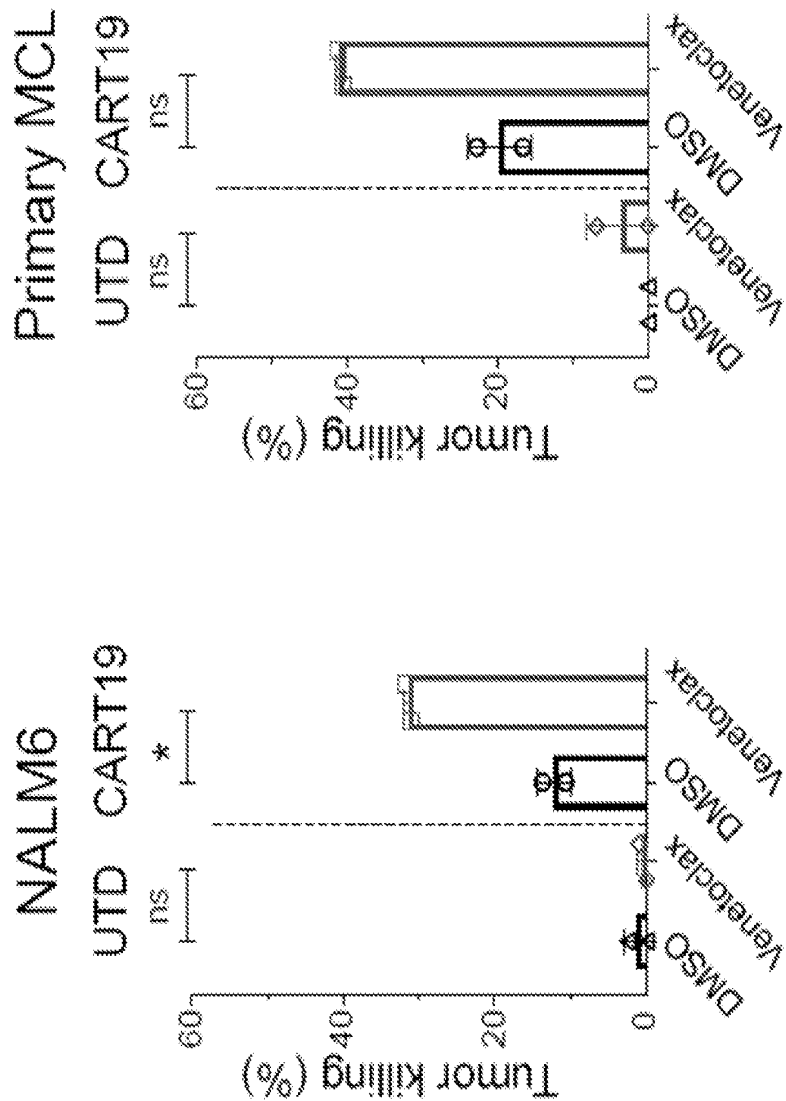


FIG. 1D – 2 of 2

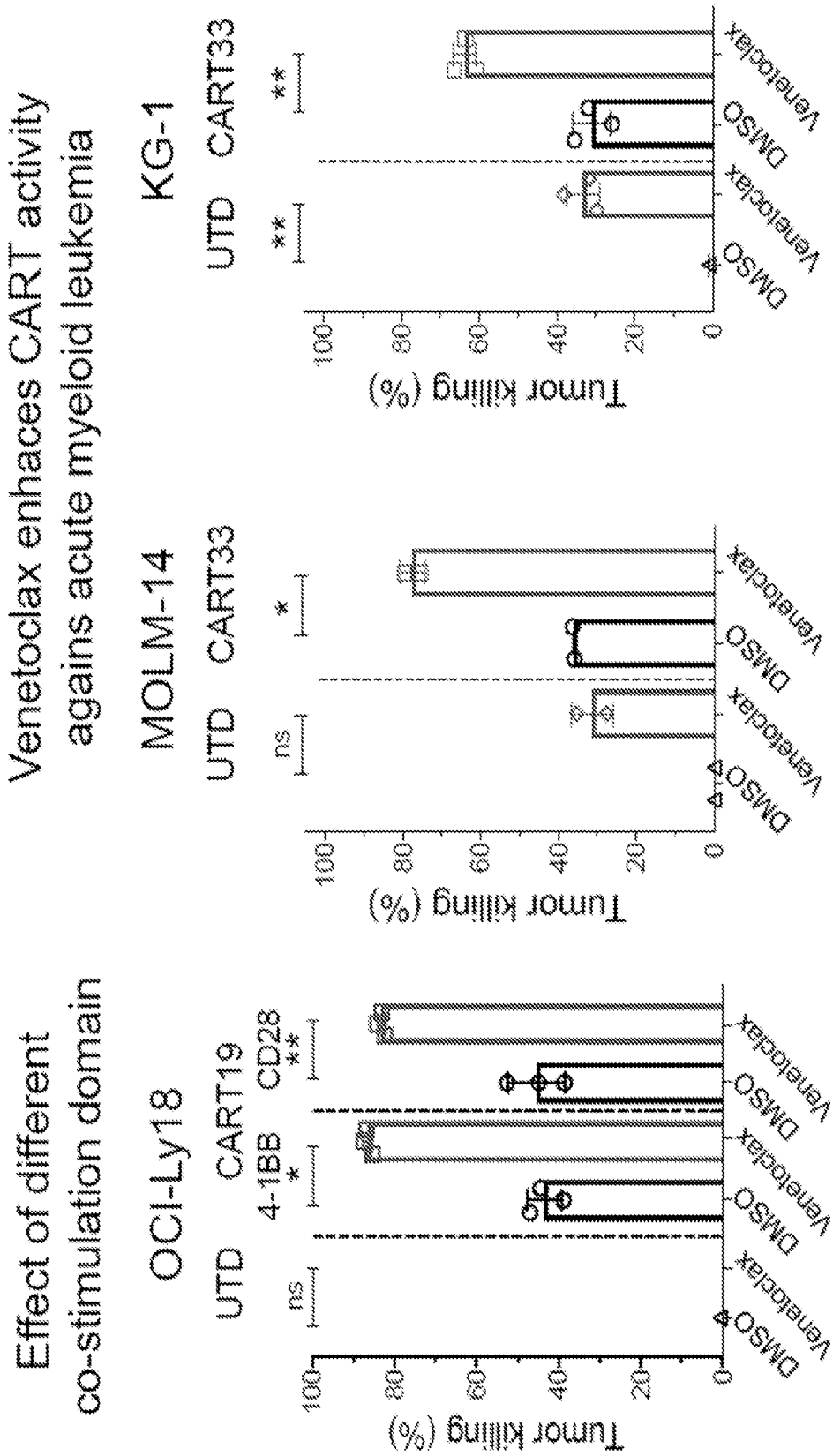


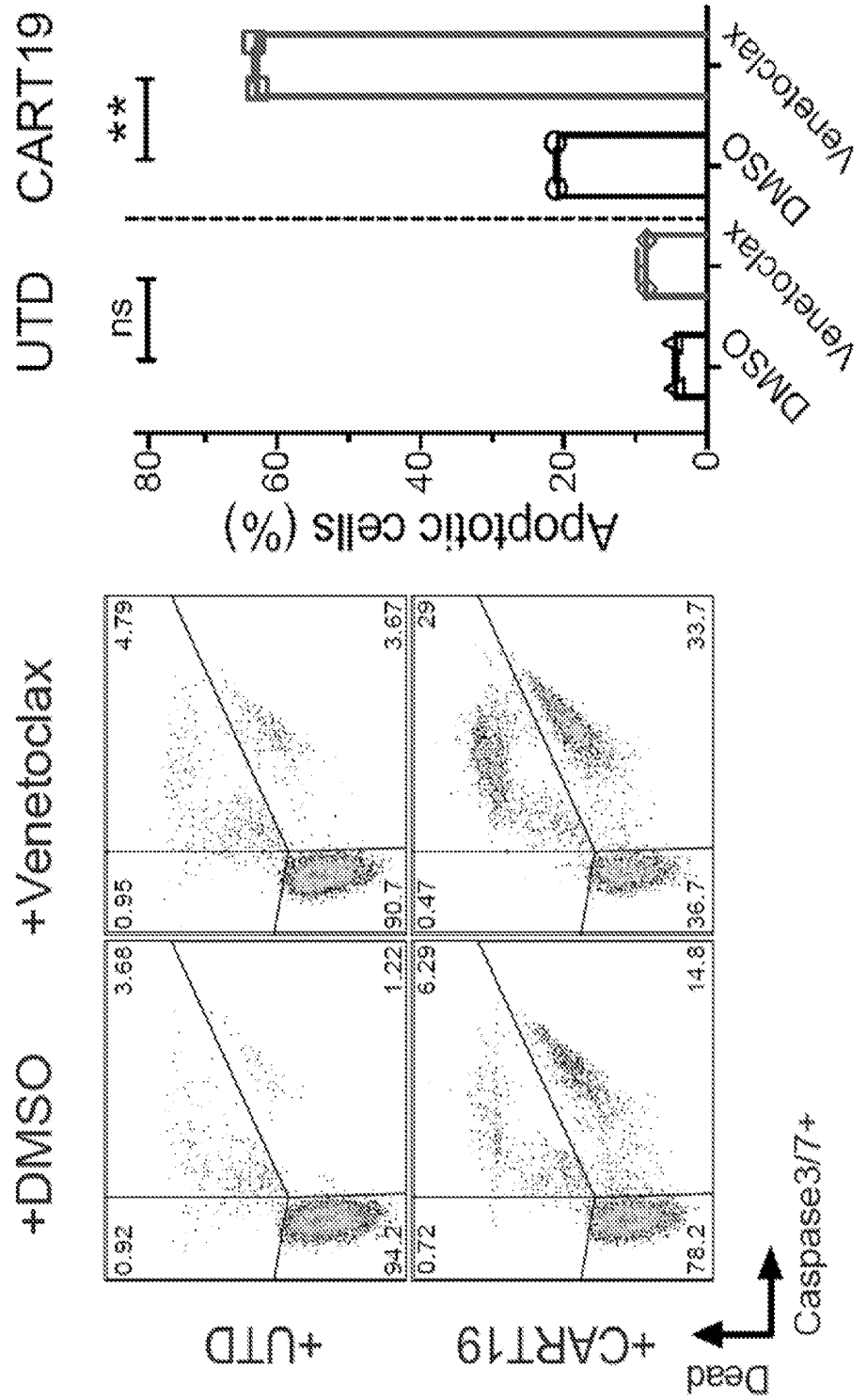
FIG. 1F

FIG. 1E

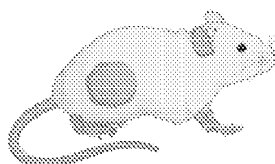
FIG. 1G

Increased caspase activity in
venetoclax-exposed tumor cells

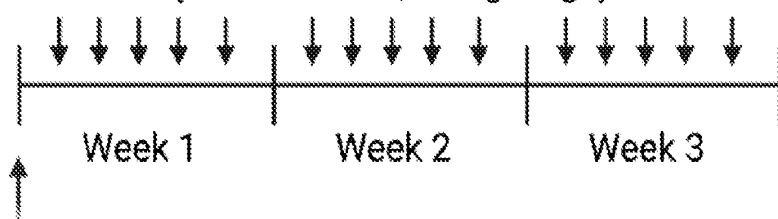
OCI-Ly18



Tumor volume:
150 mm³



Vehicle (5 times/week, oral gavage)



UTD or CART19

↓ Venetoclax (25mg/kg, 5 times/week, oral gavage)

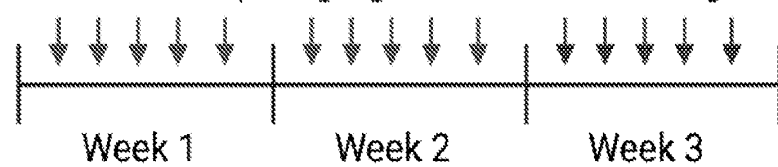


FIG. 1H – 1 of 3

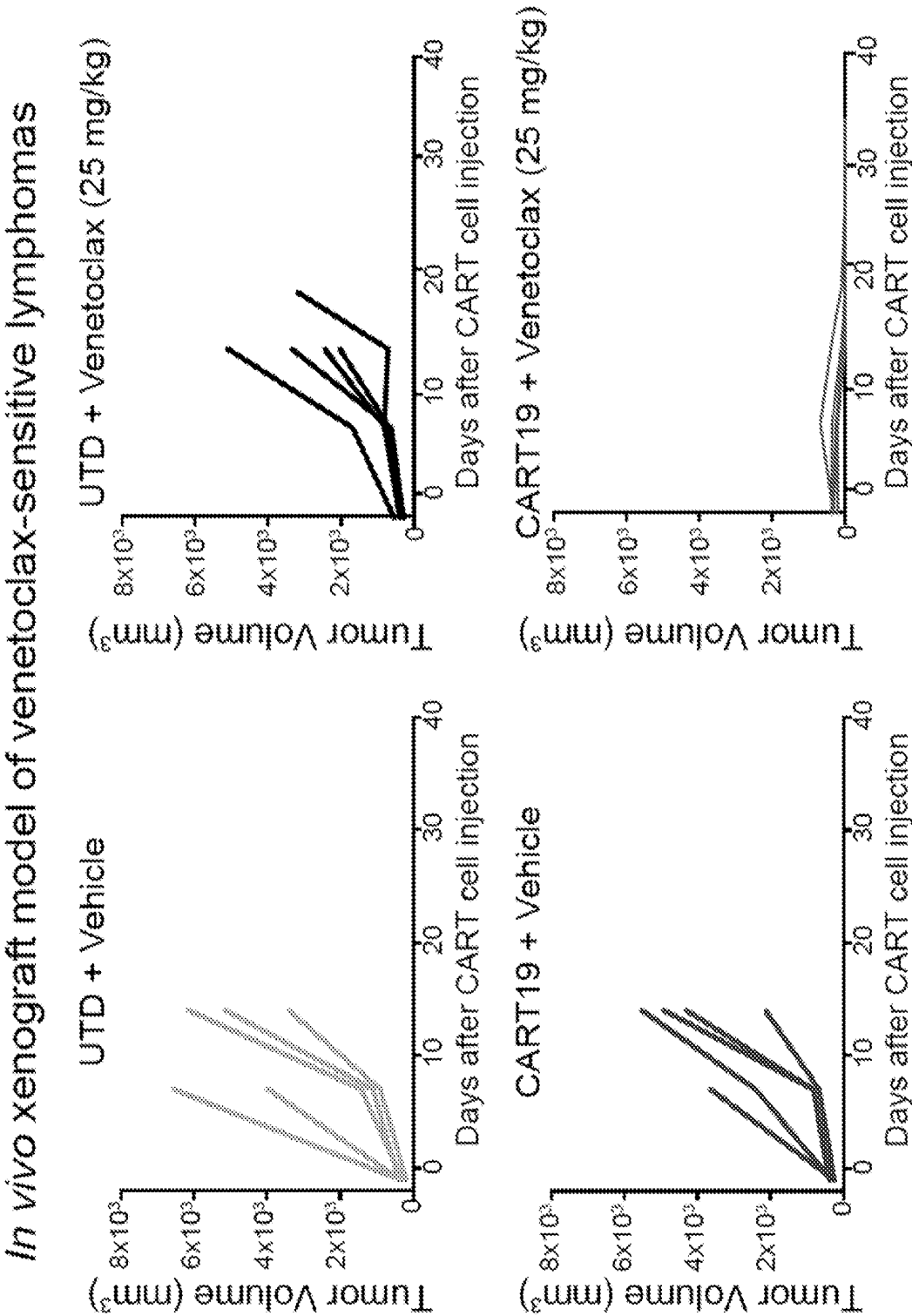


FIG. 1H – 2 of 3

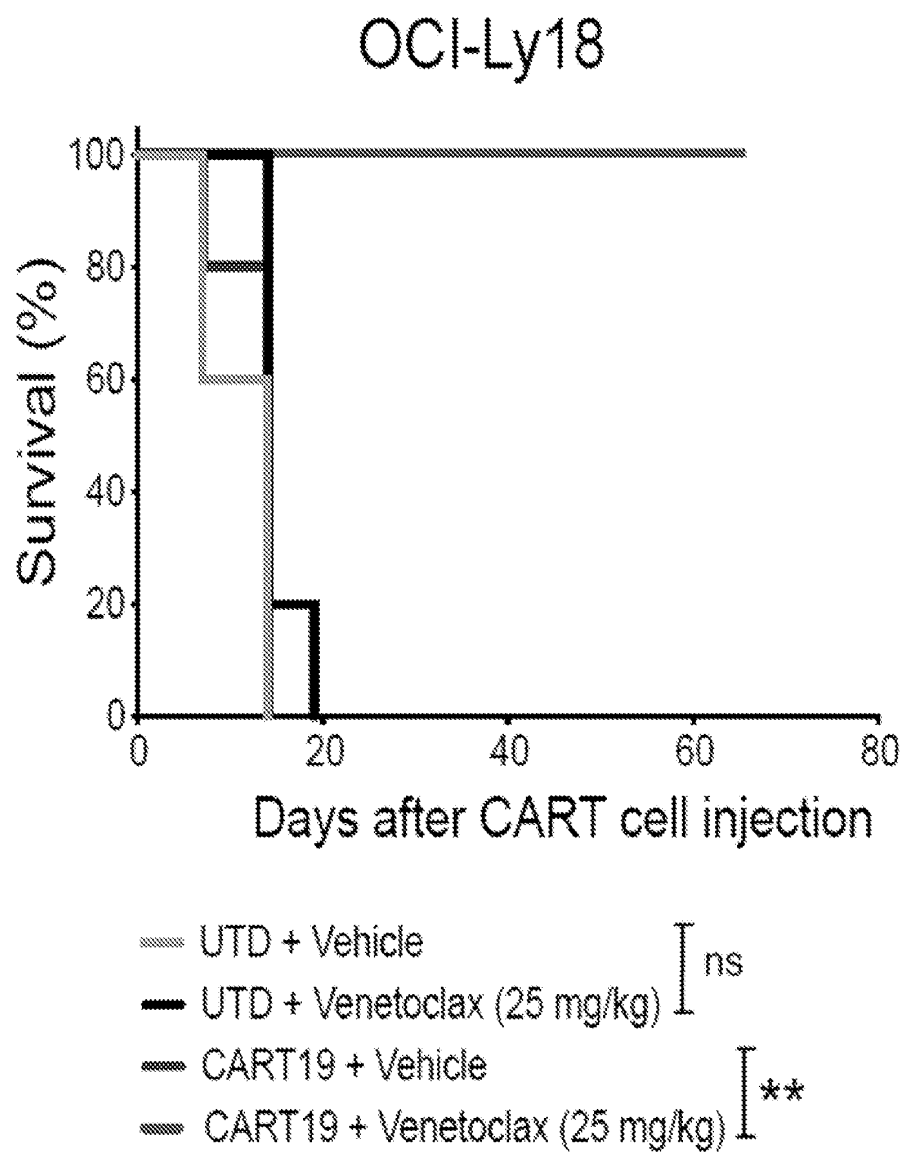


FIG. 1H – 3 of 3

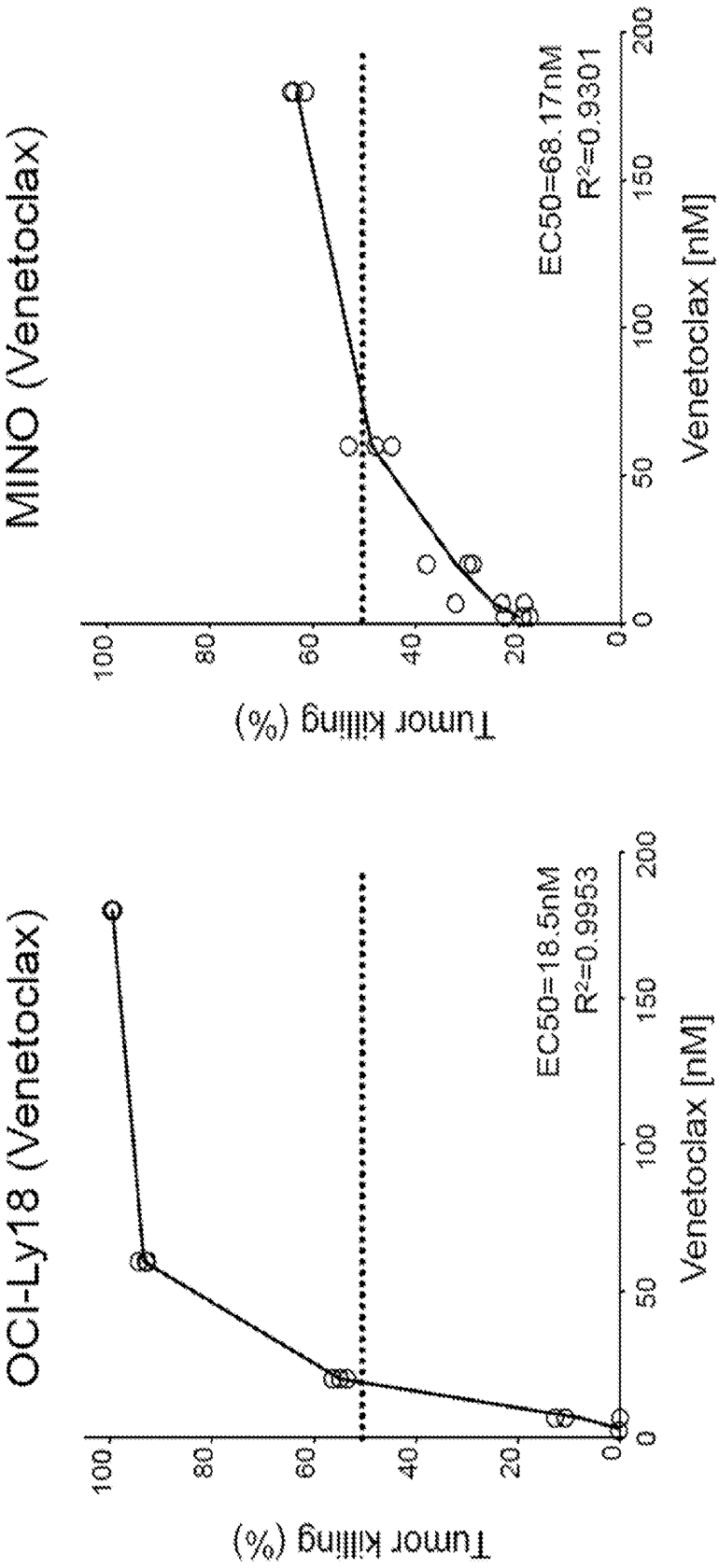


FIG. 2A

FIG. 2B

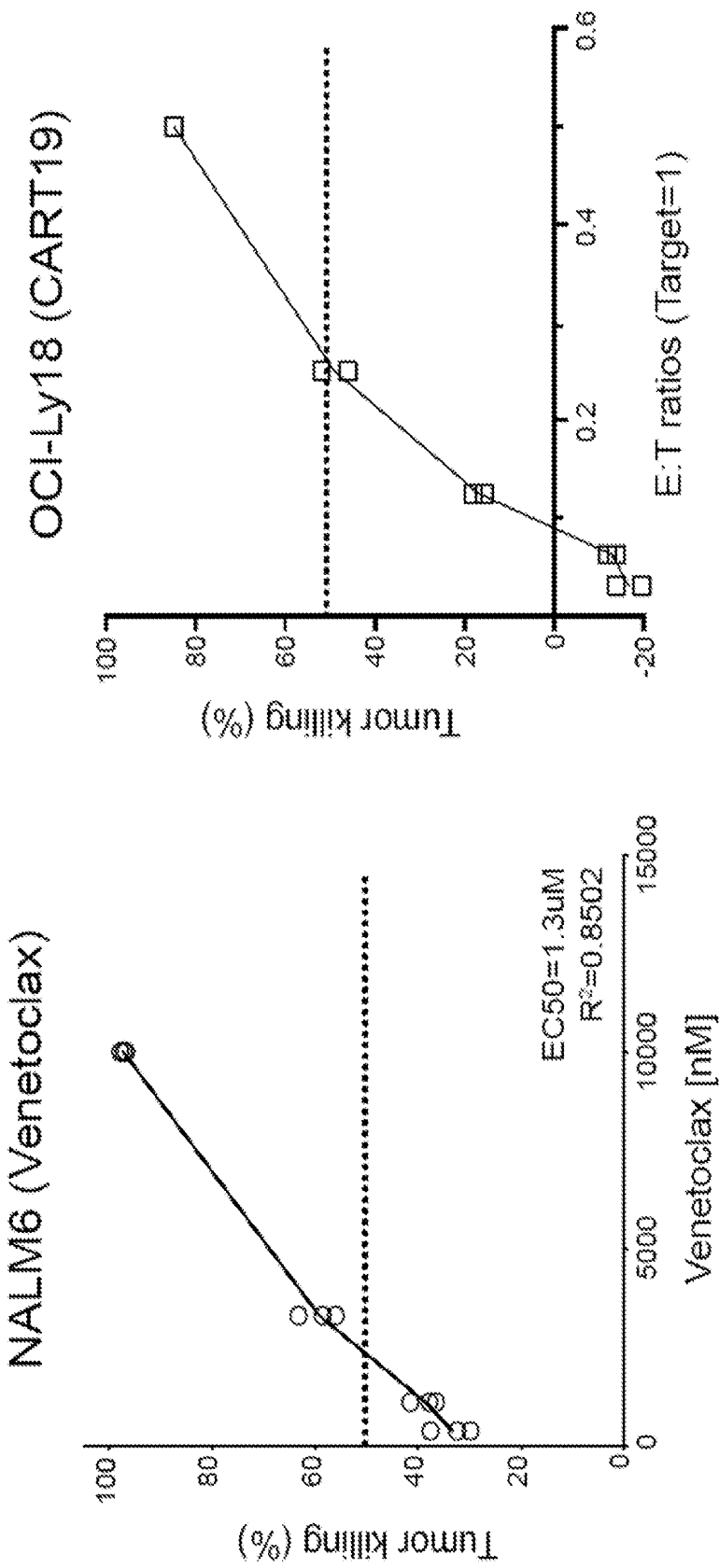


FIG. 2C

FIG. 2D

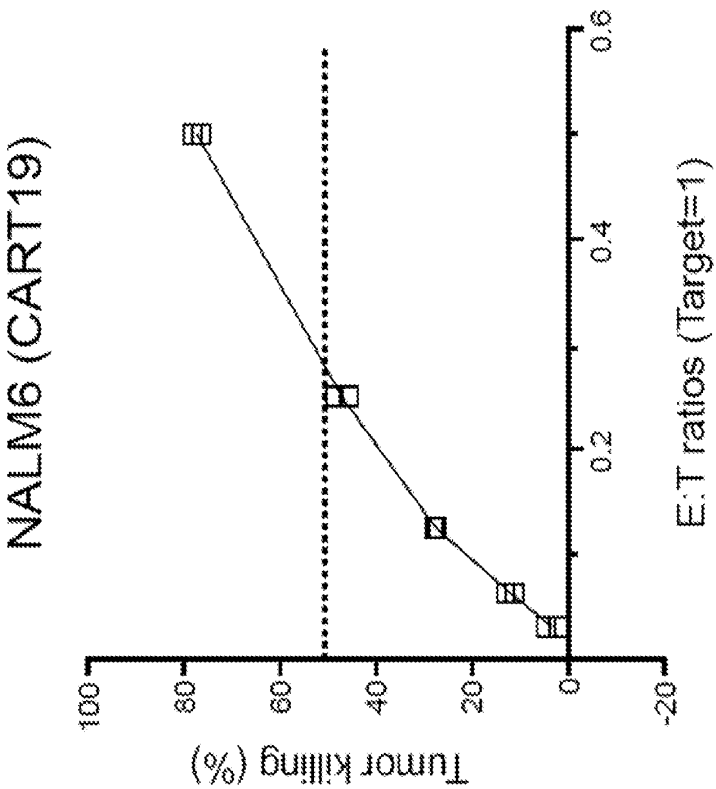


FIG. 2F

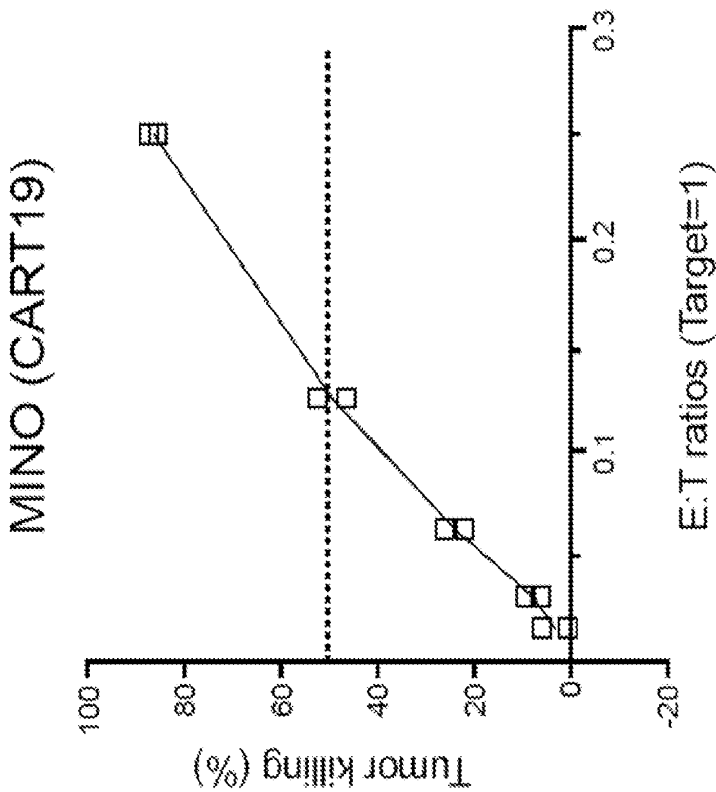


FIG. 2E

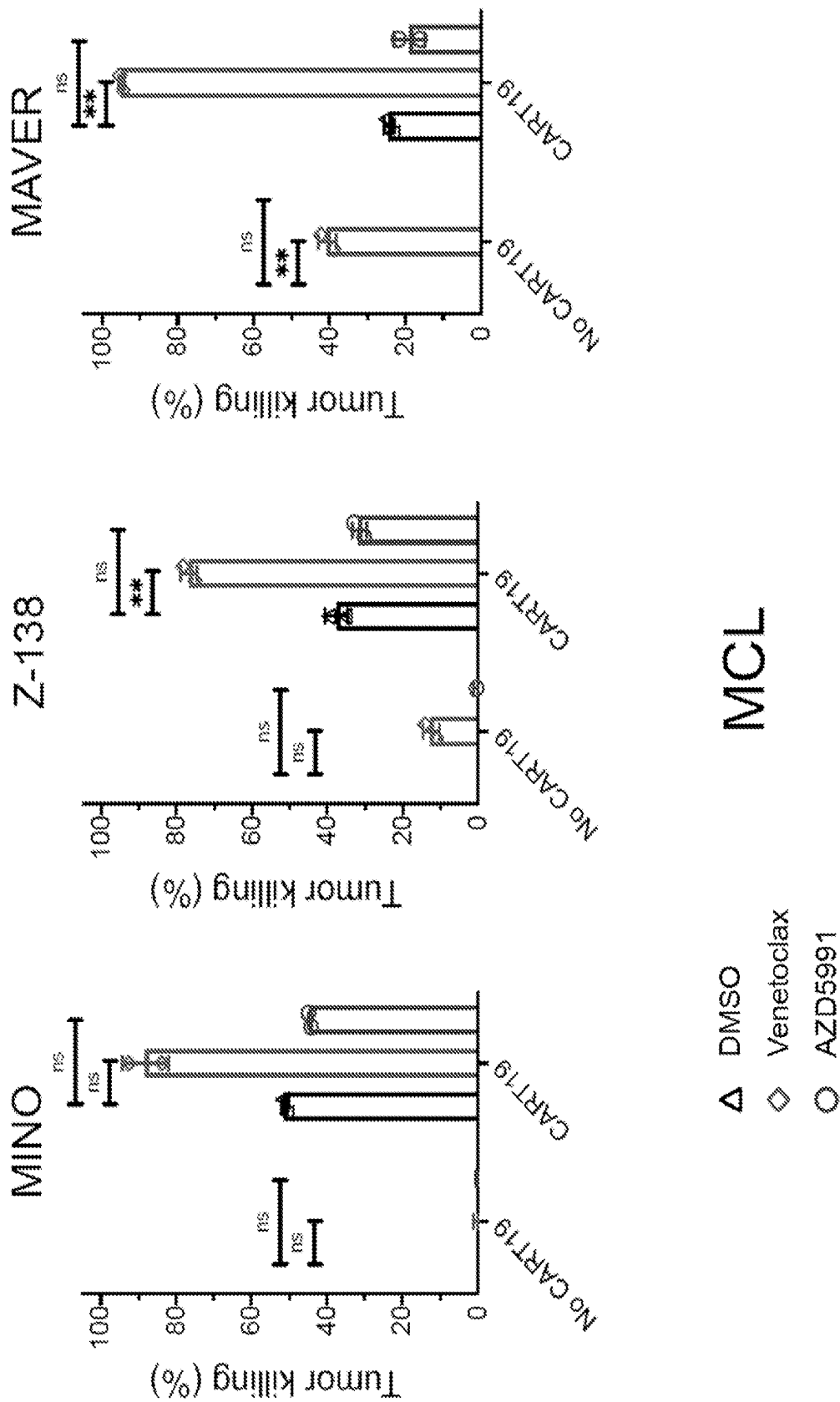


FIG. 3 – 1 of 3



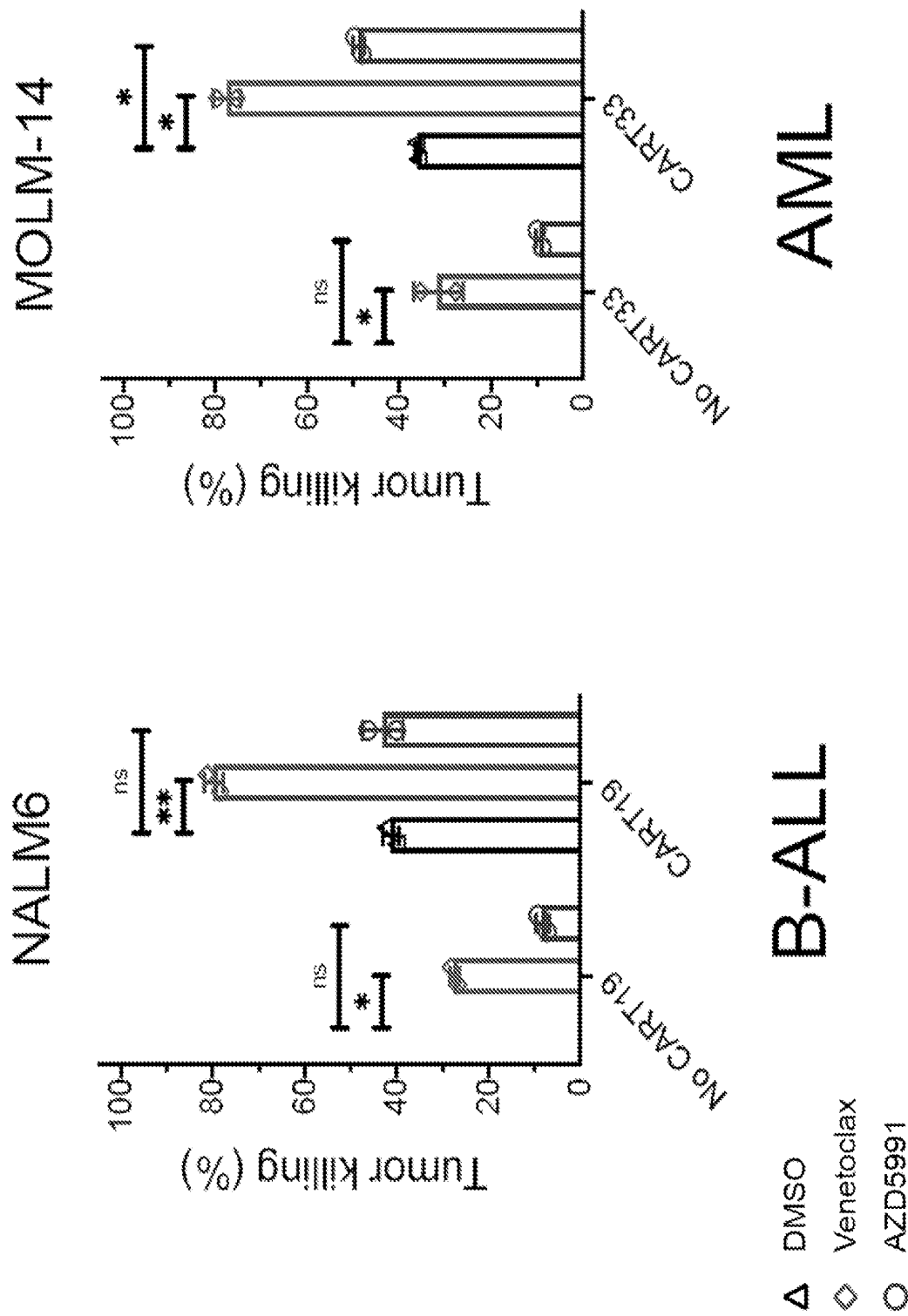


FIG. 3 – 3 of 3

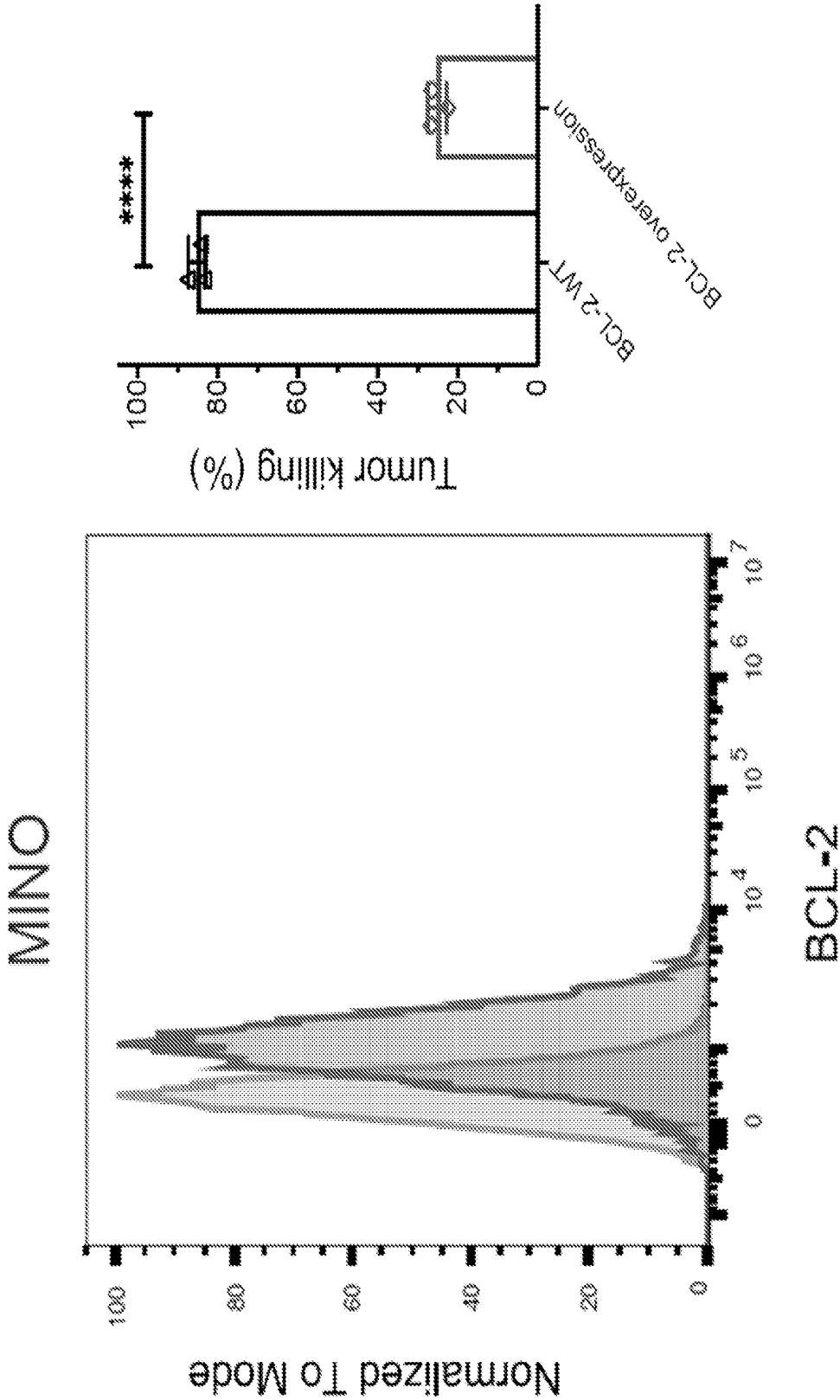


FIG. 4A

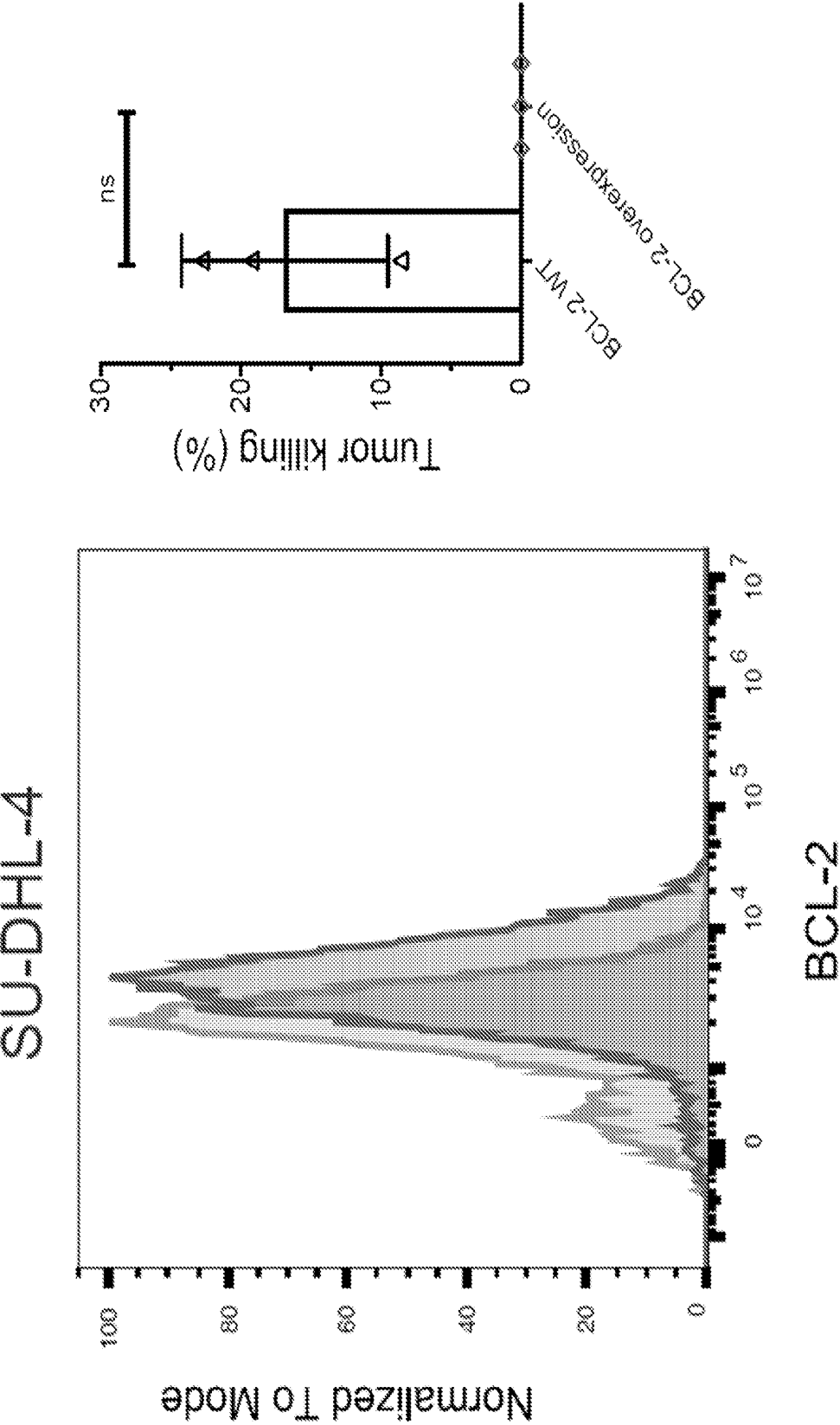


FIG. 4B

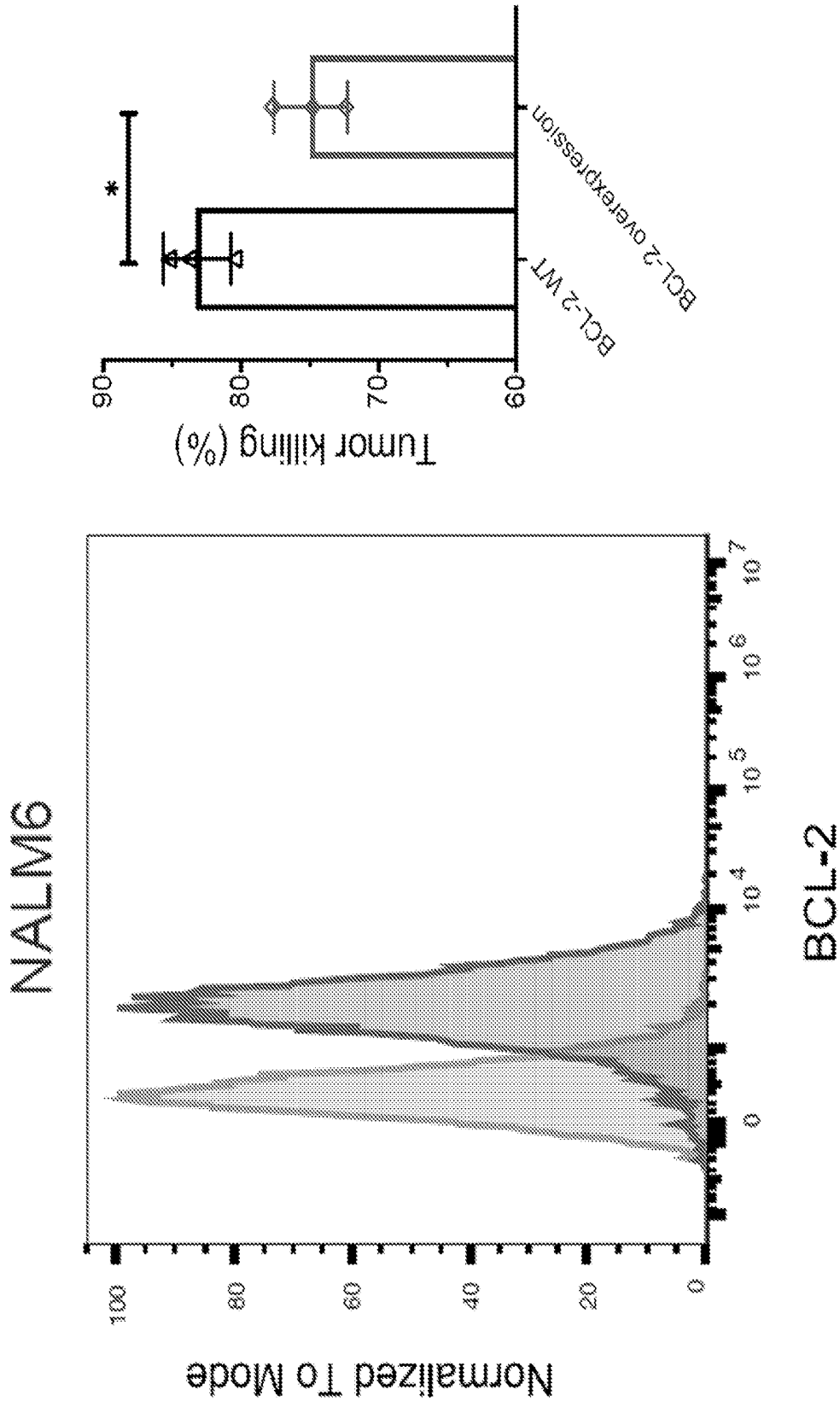


FIG. 4C

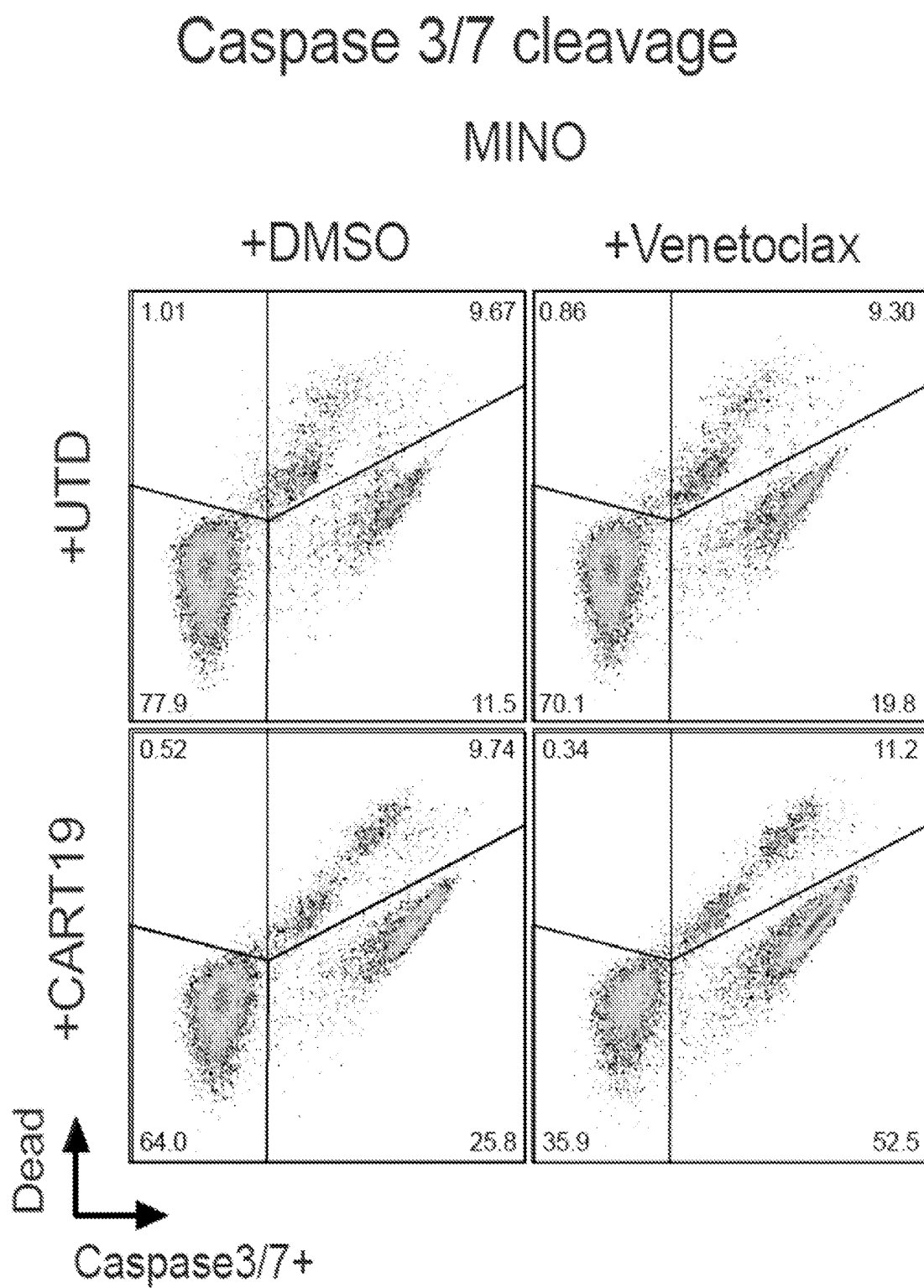


FIG. 5A

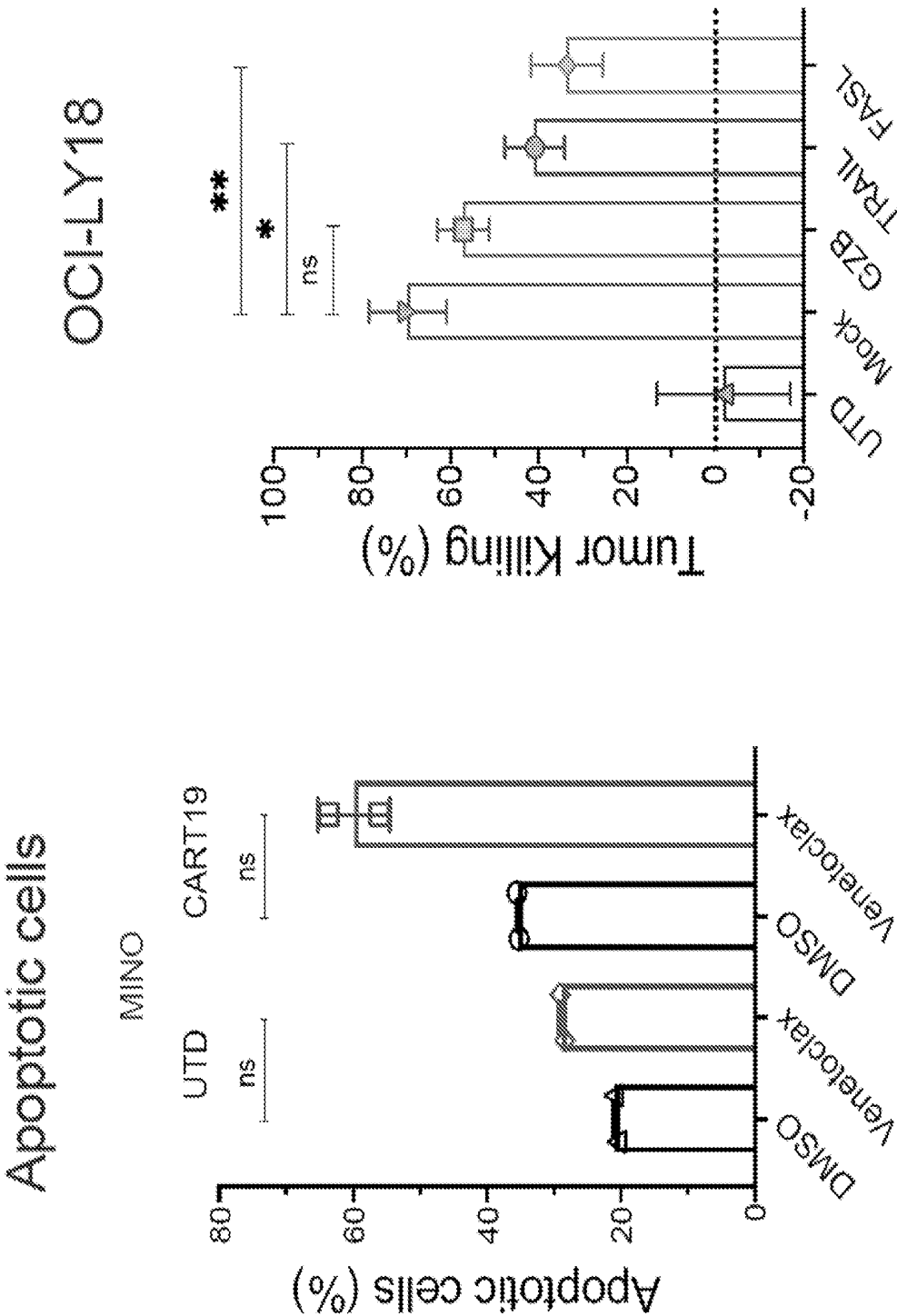


FIG. 5C

FIG. 5B

In vivo xenograft model of lymphoma:
tumor scRNA-seq

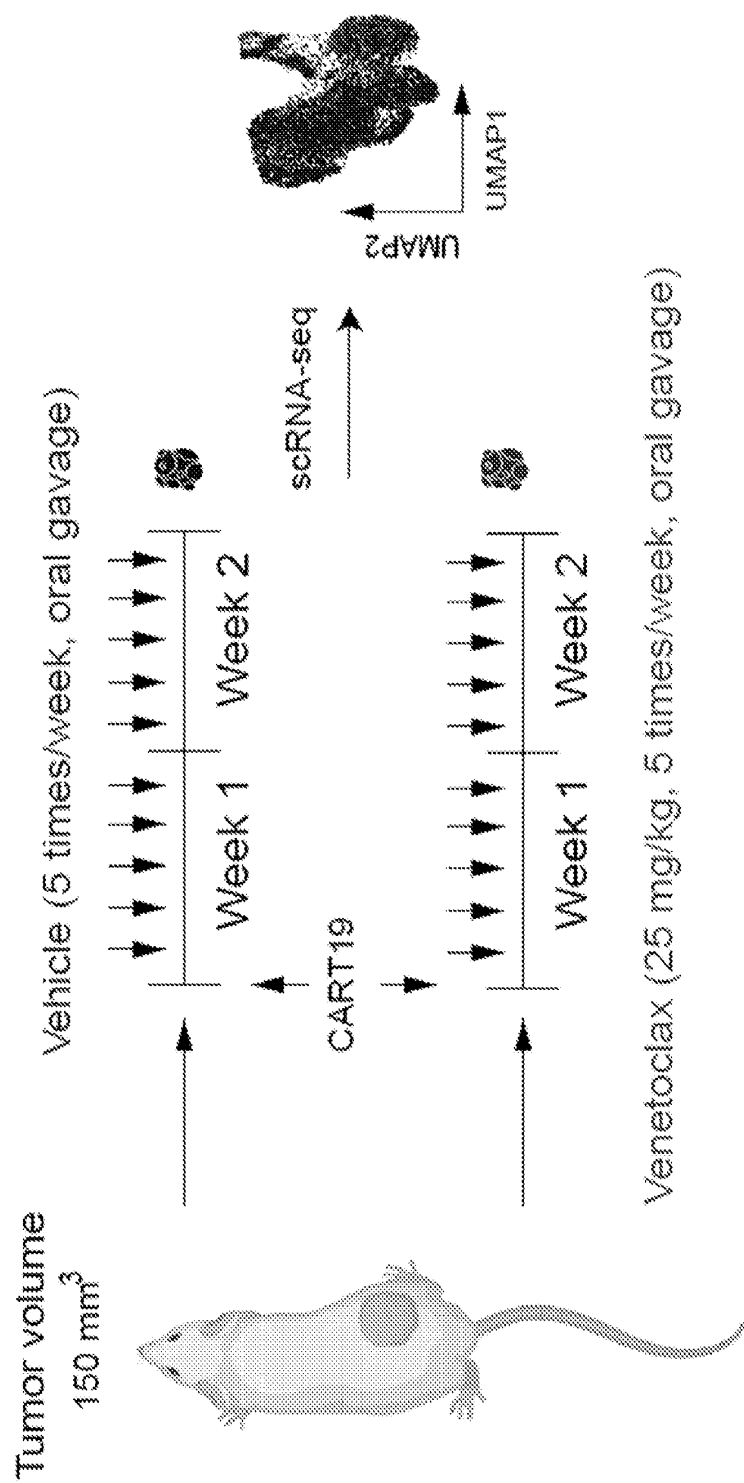


FIG. 6A

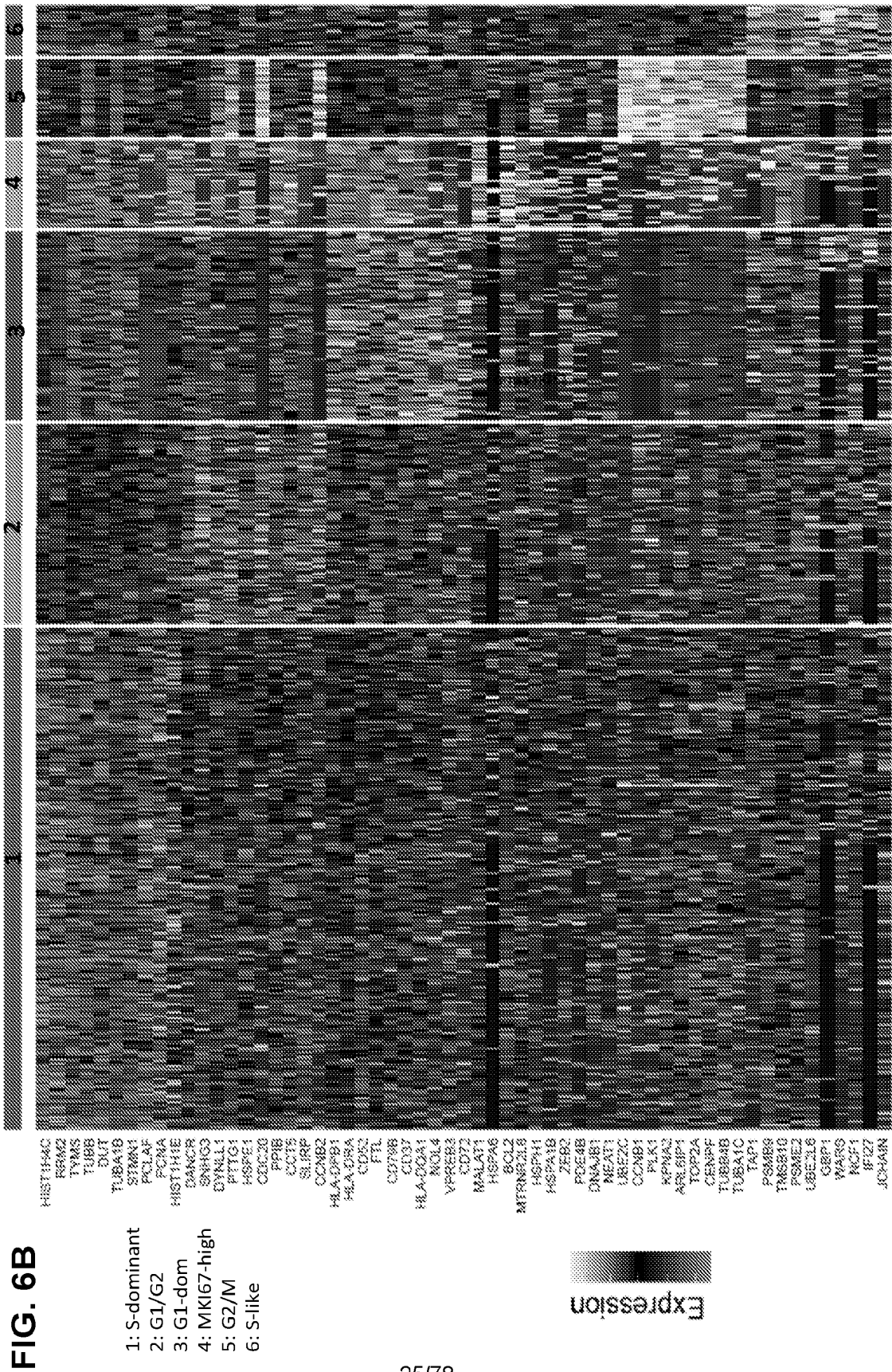


FIG. 6C

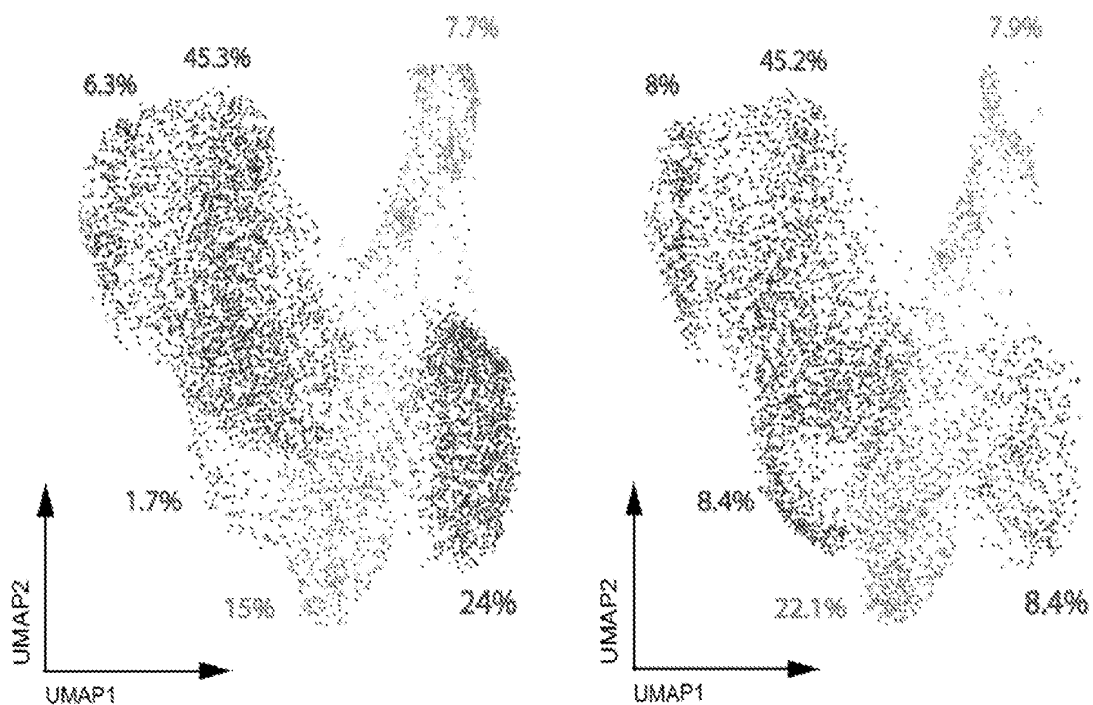
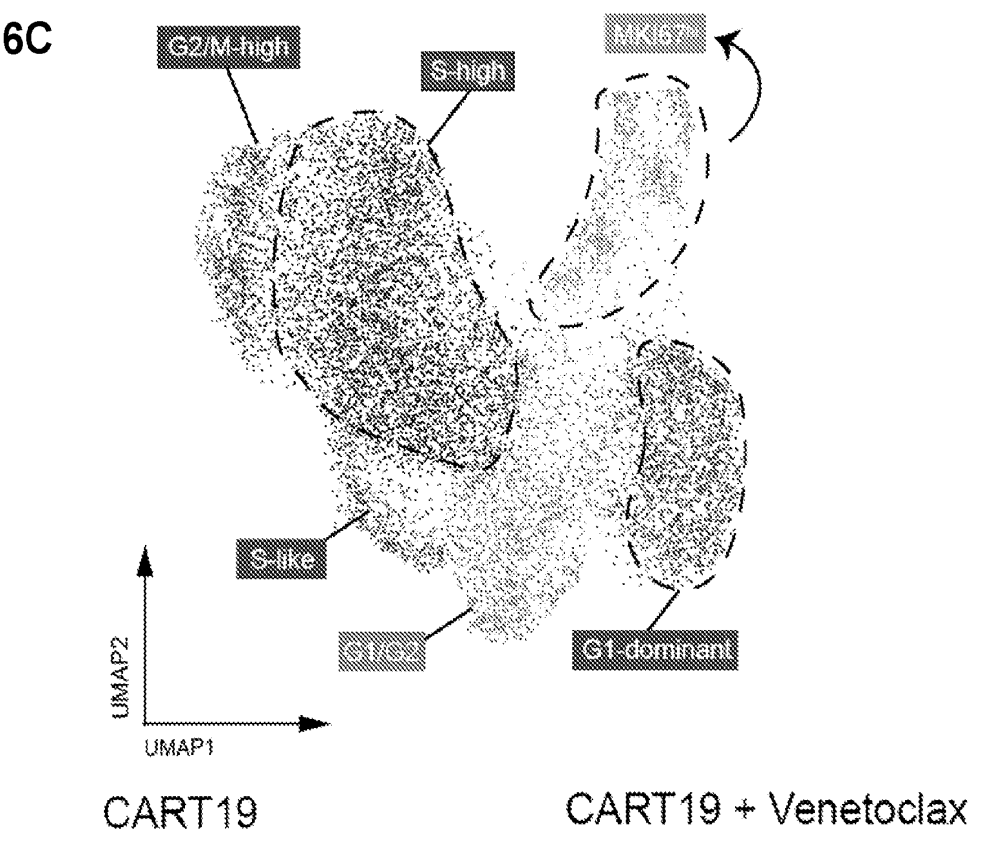
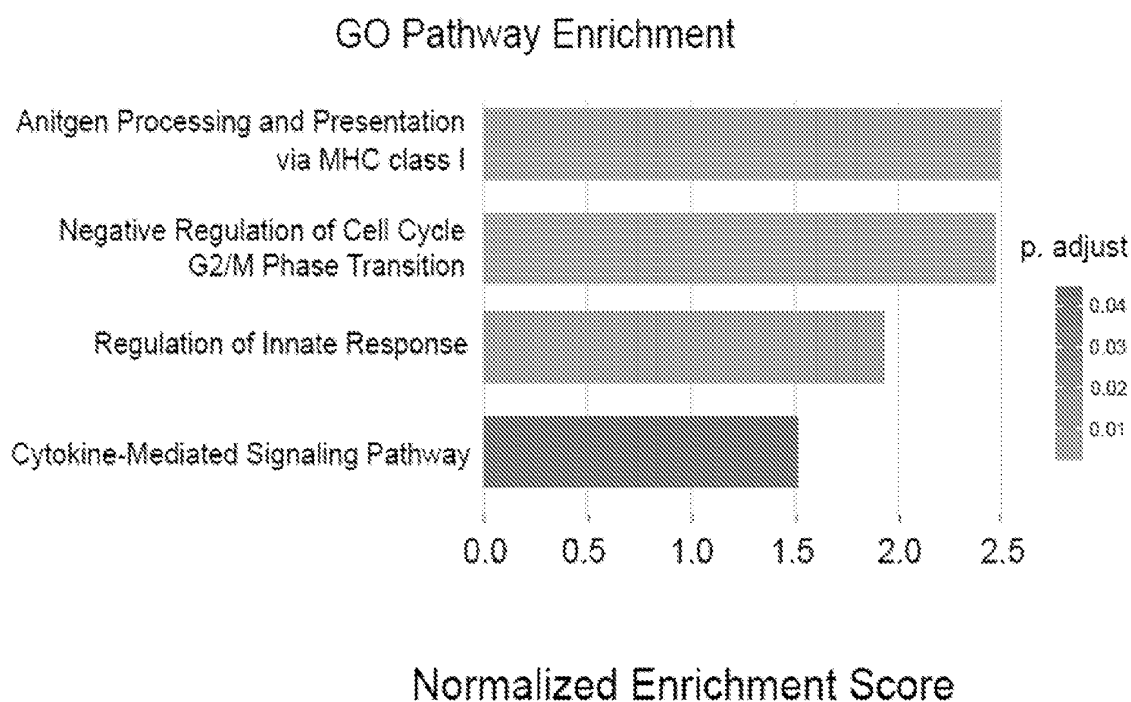
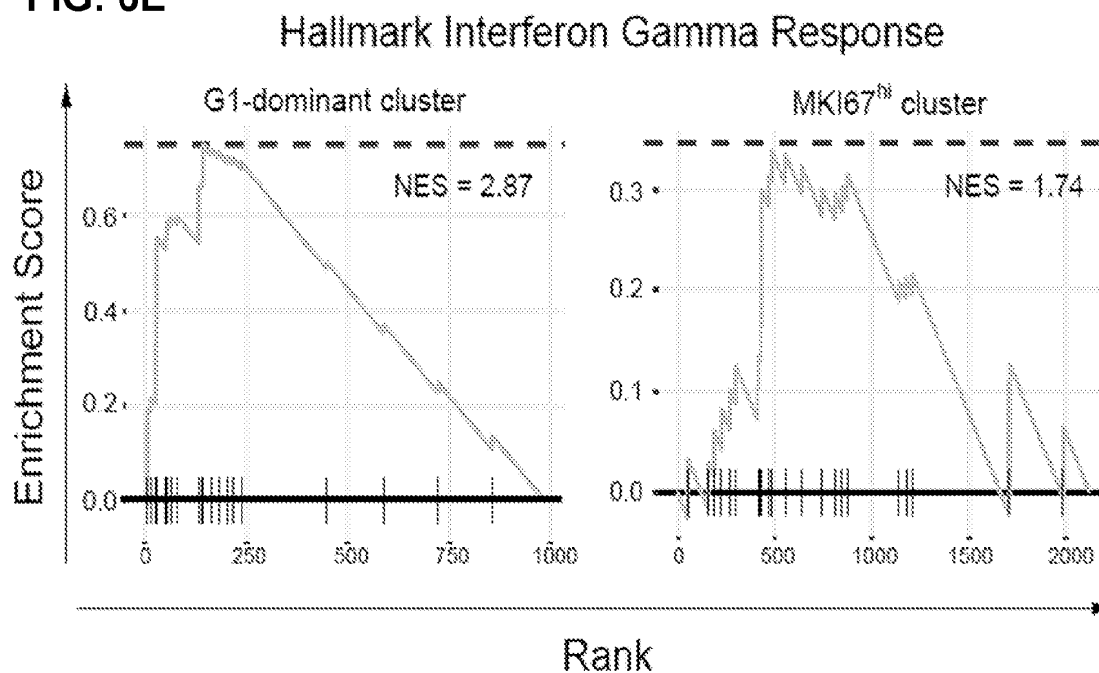


FIG. 6D

FIG. 6E**FIG. 6F**

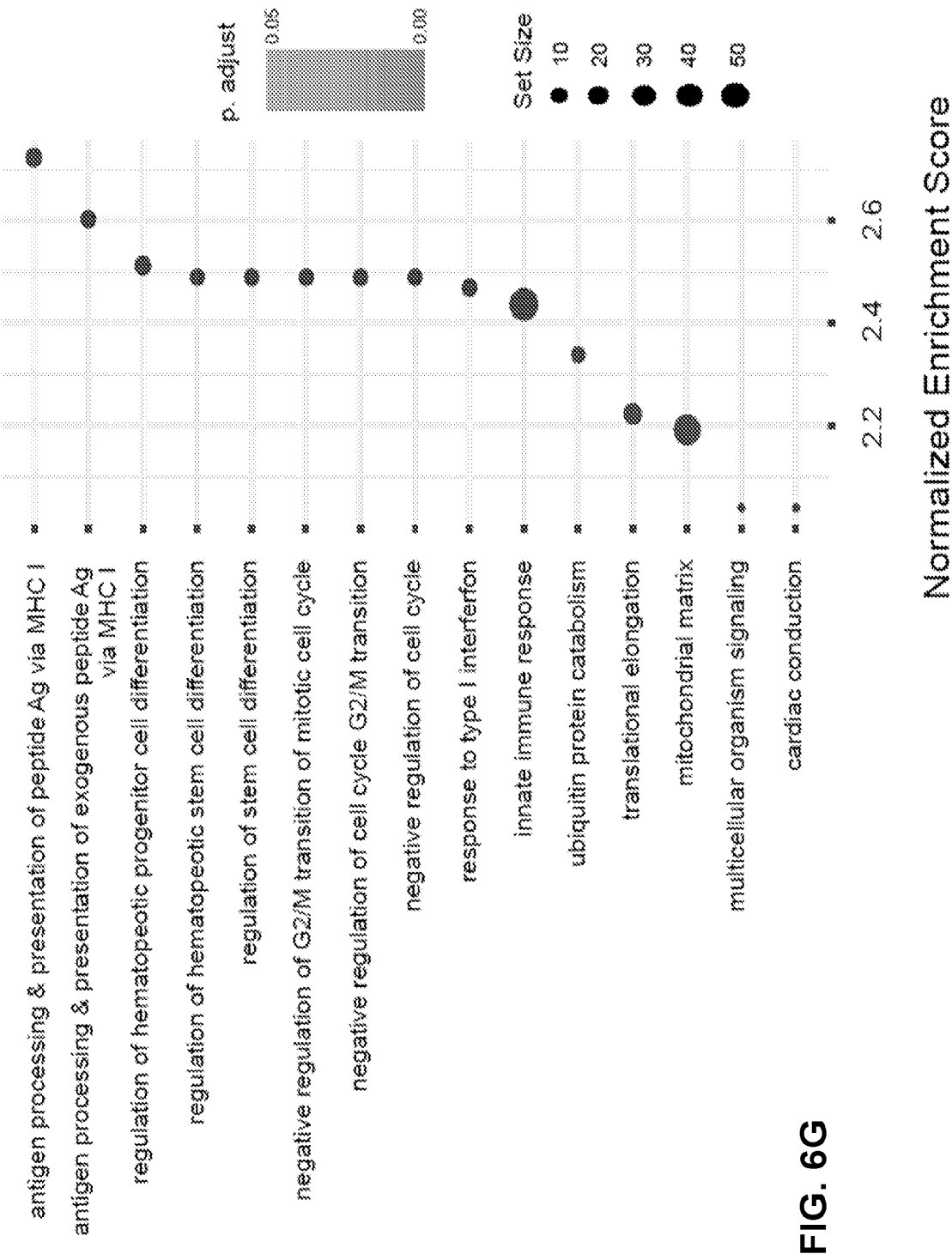


FIG. 6G

FIG. 7A

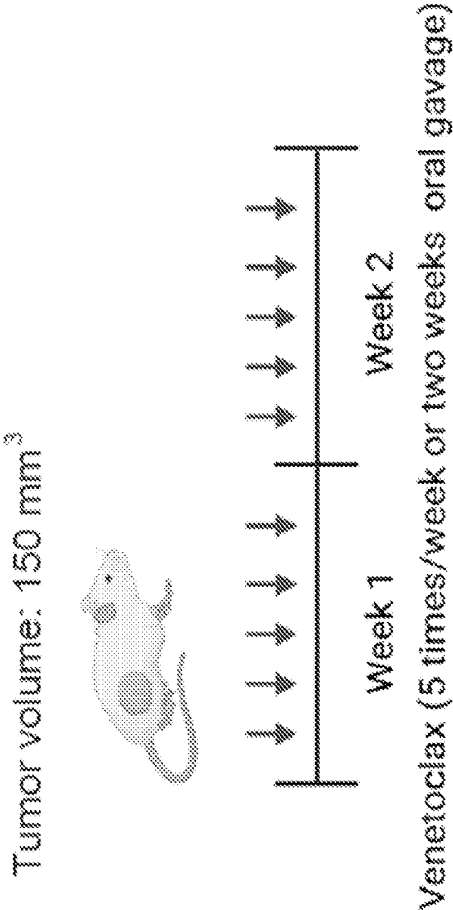
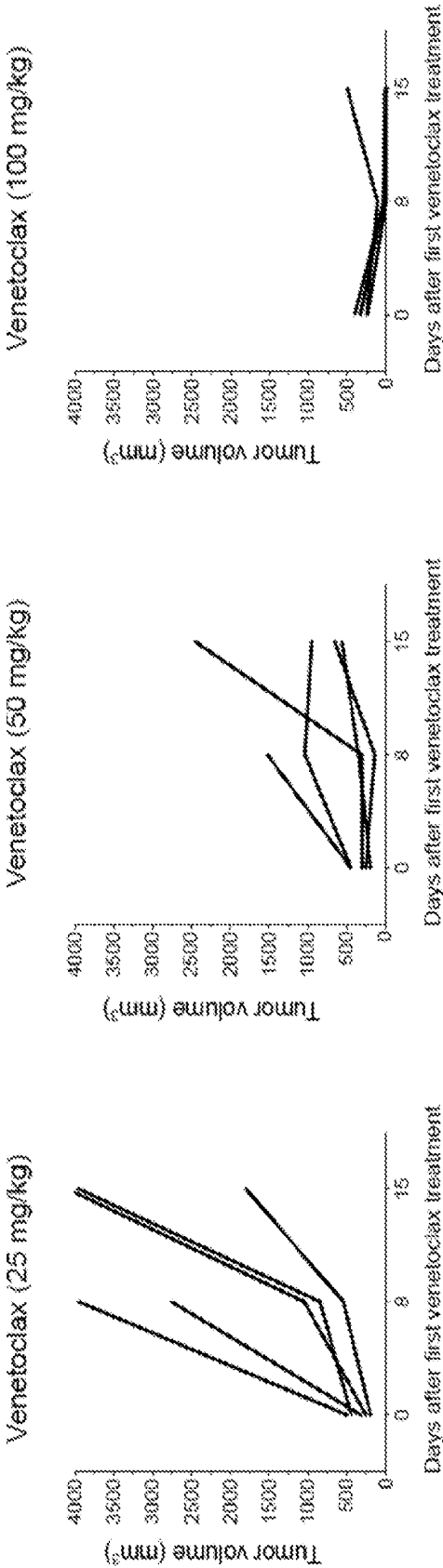


FIG. 7B



In vivo xenograft model of venetoclax-resistant lymphomas

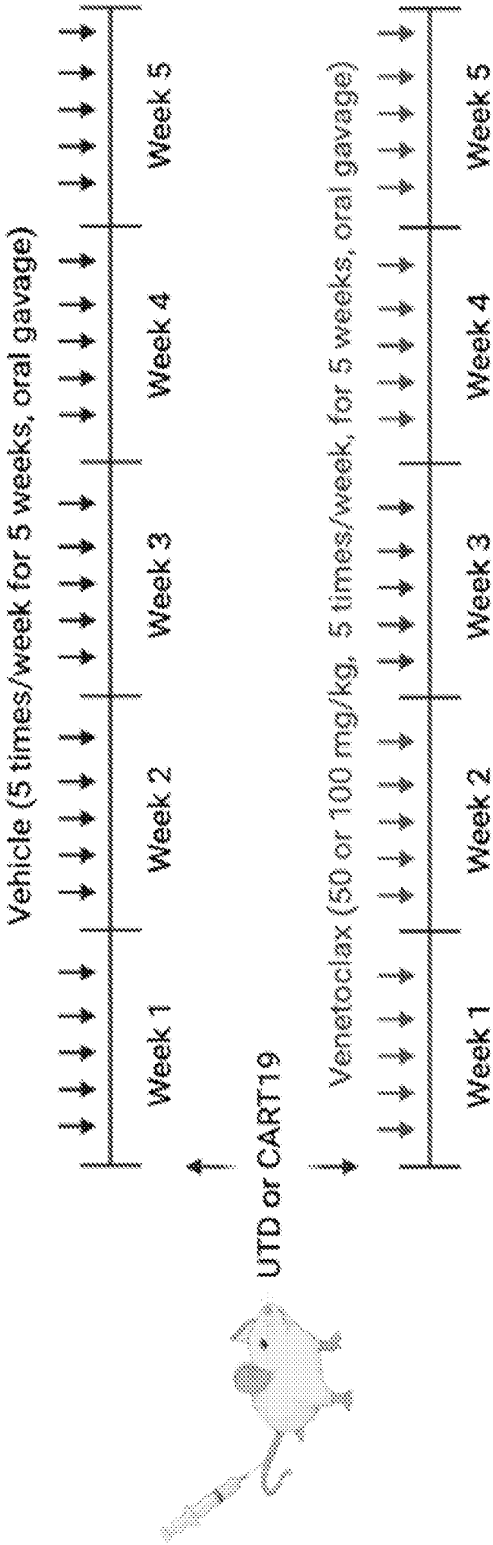


FIG. 8A

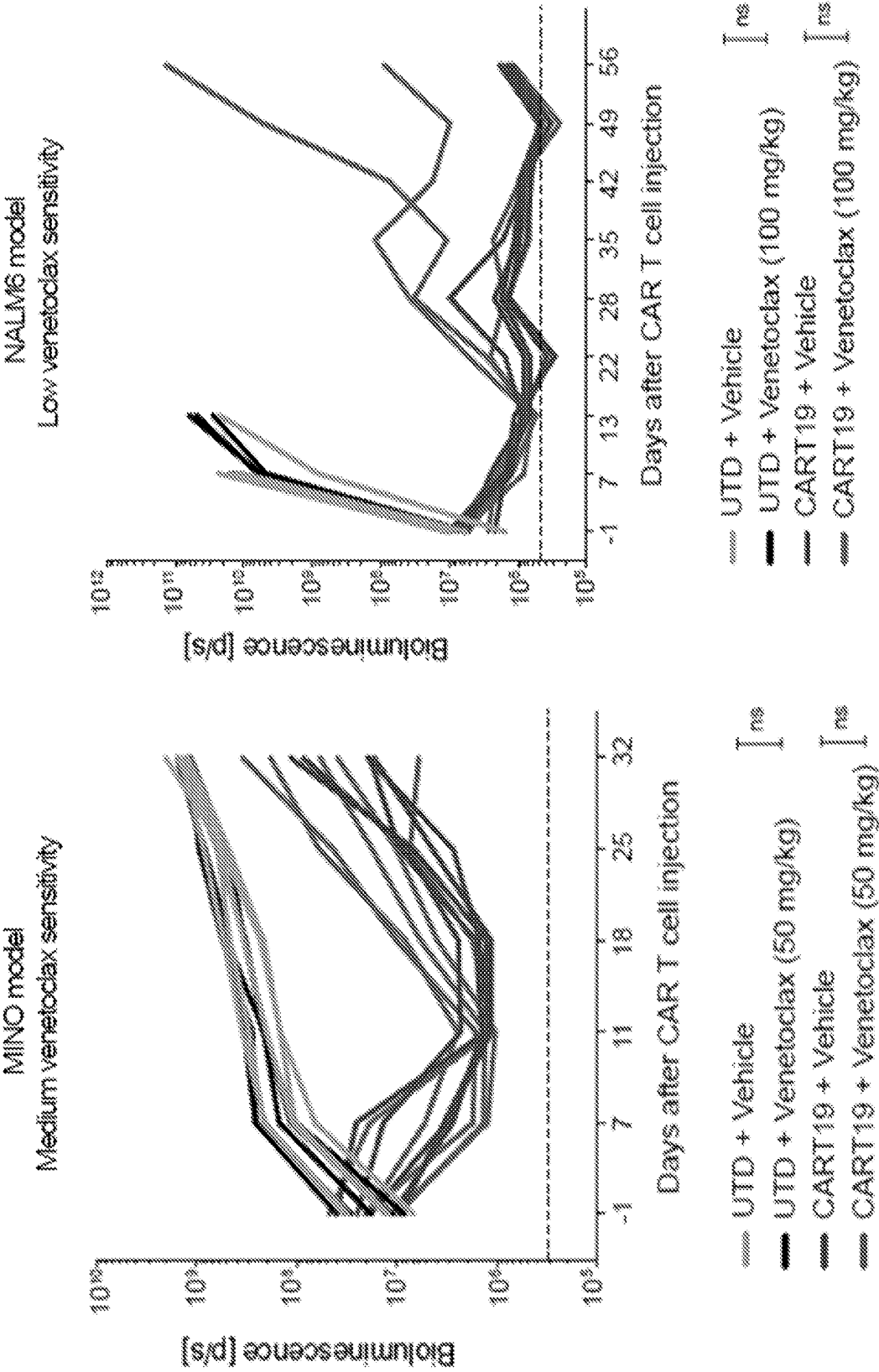


FIG. 8B

FIG. 8C

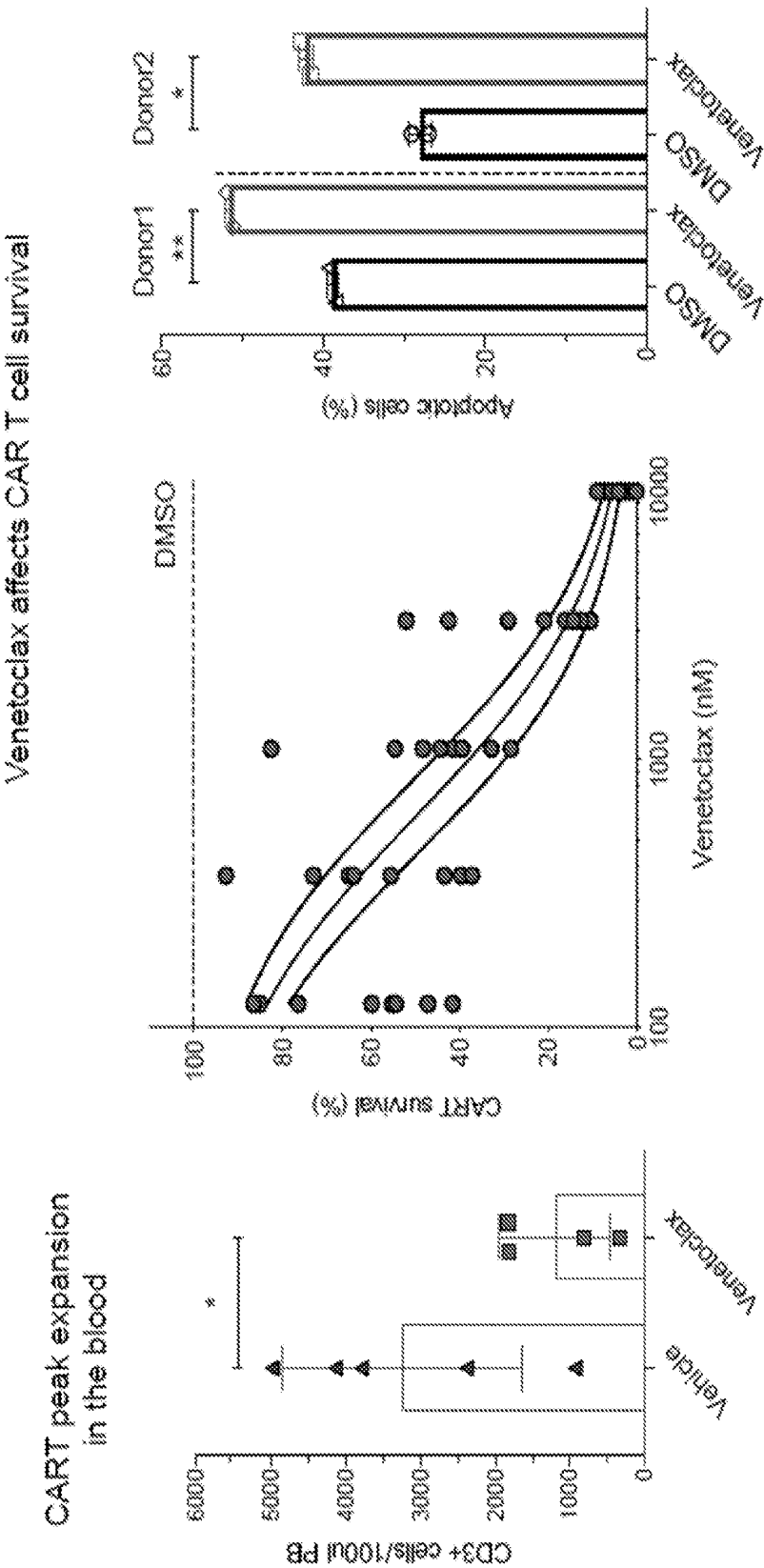
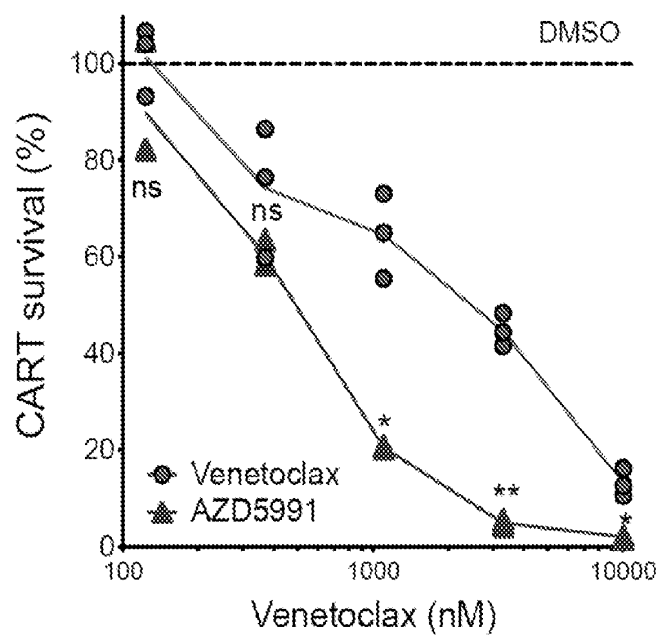
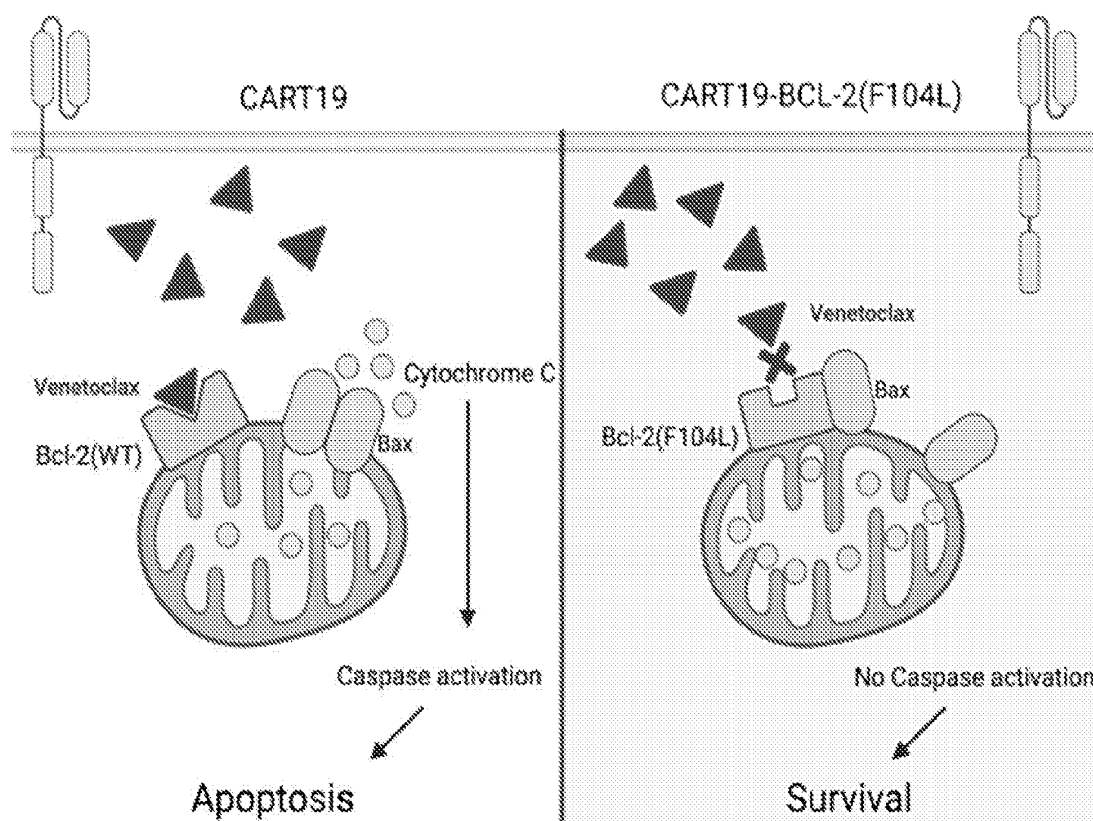


FIG. 8E

FIG. 8D

FIG. 9

Development of venetoclax-resistant CART cells

**FIG. 10A**

Cytotoxicity of CART19-BCL-2(F104L)
against NHL

MINO

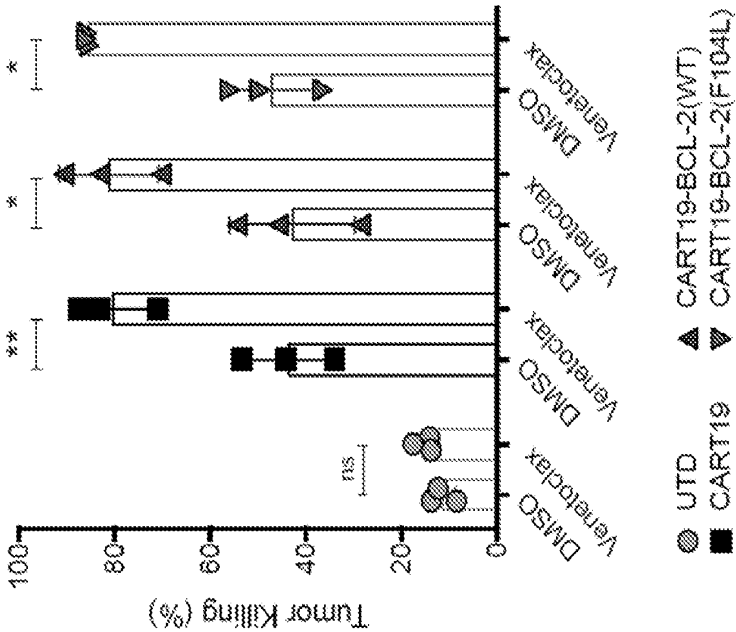


FIG. 10C

BCL-2 expression in CART cells

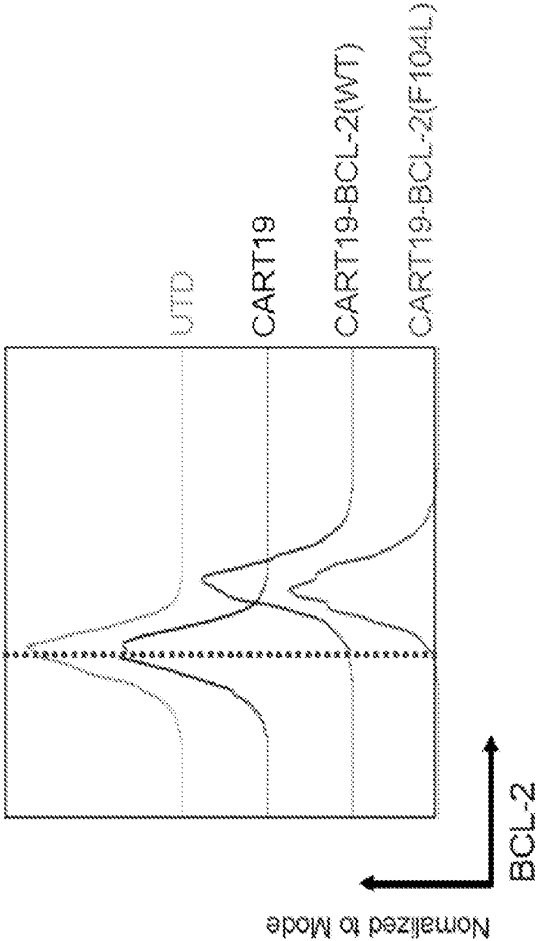
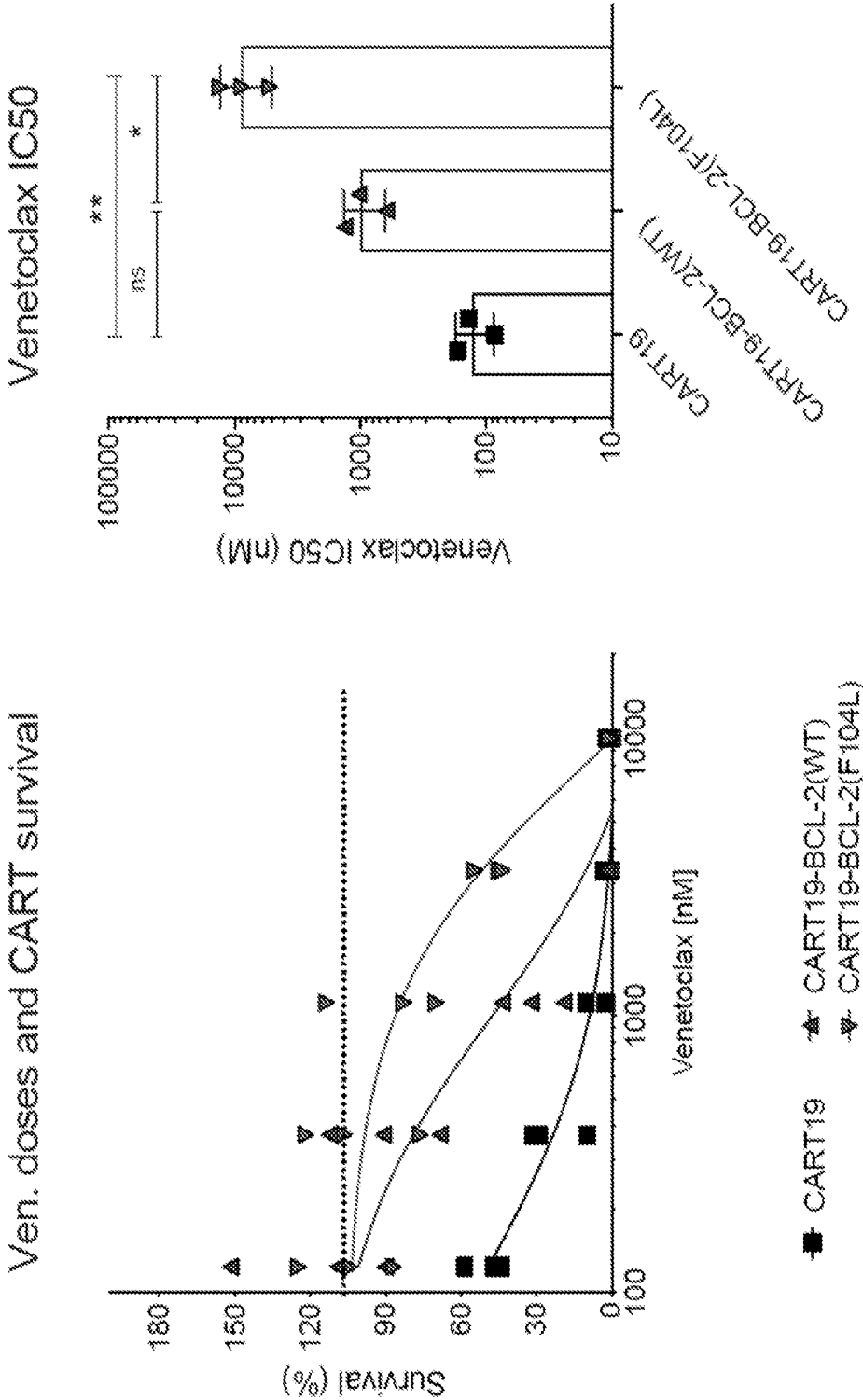


FIG. 10B

BCL-2(F104L) prevents venetoclax-mediated CART cells toxicity



Expression of BCL-2(F104L) in CART cells drives synergy against non-Hodgkin lymphoma *in vivo*

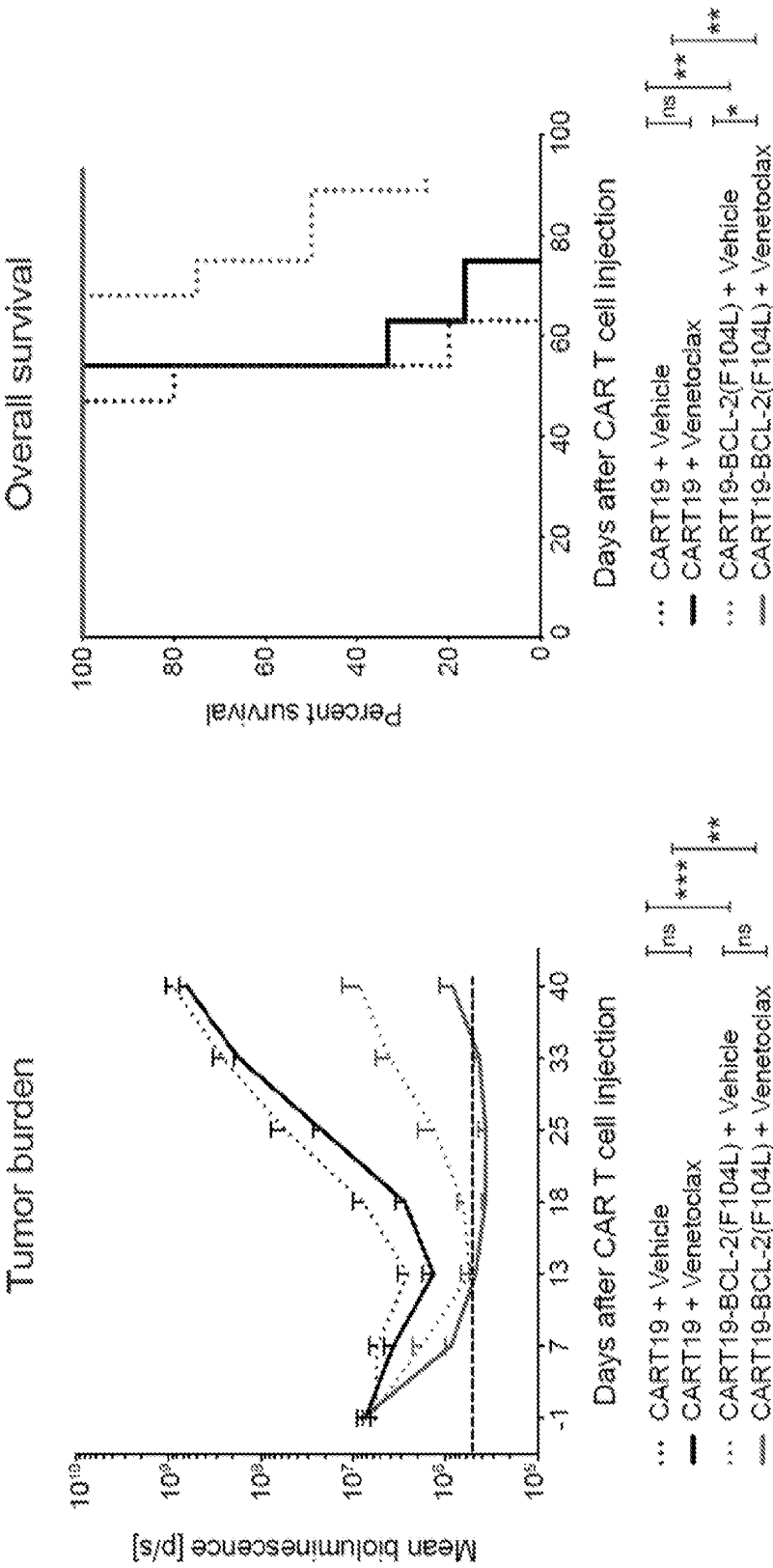


FIG. 10E

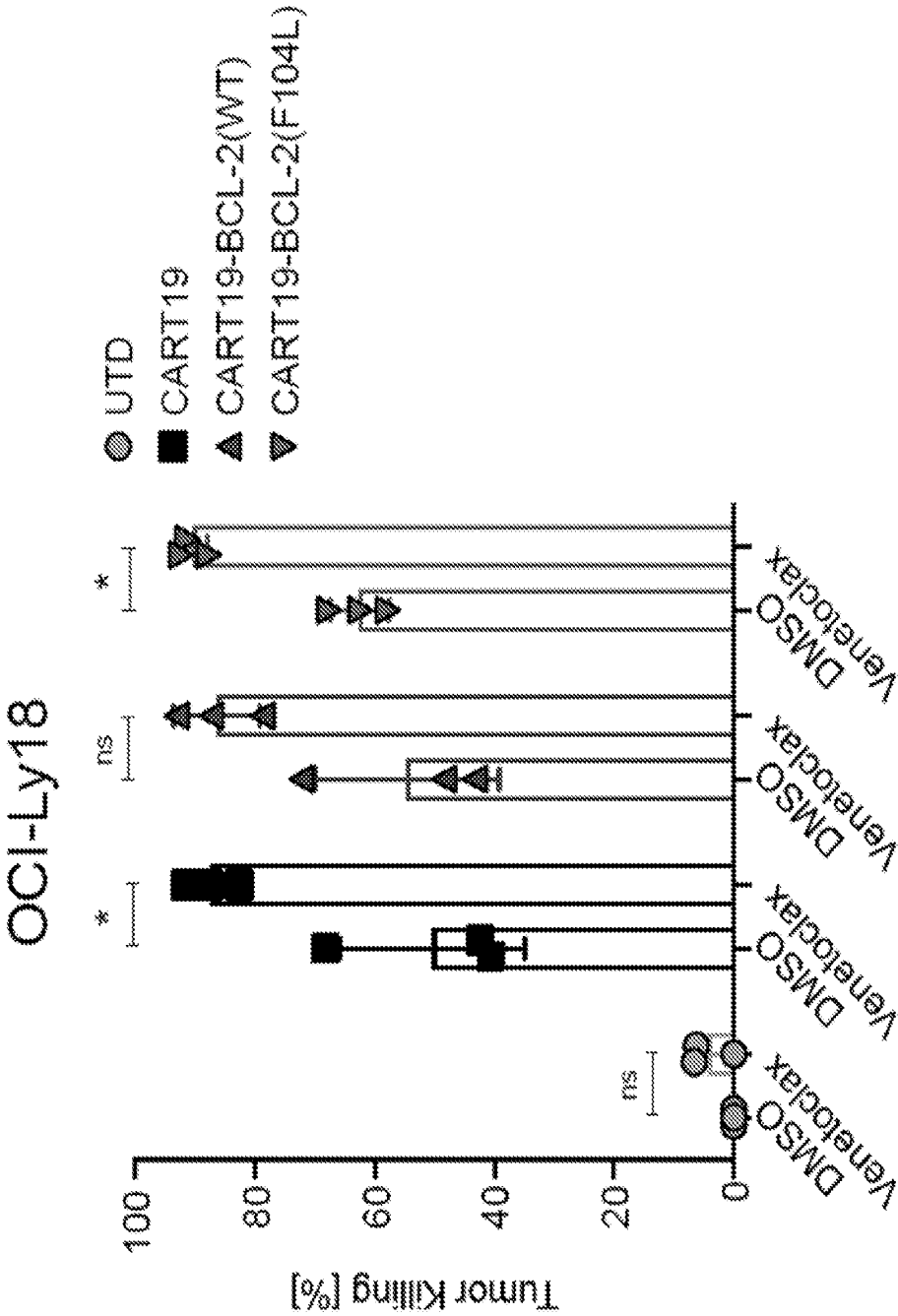


FIG. 11

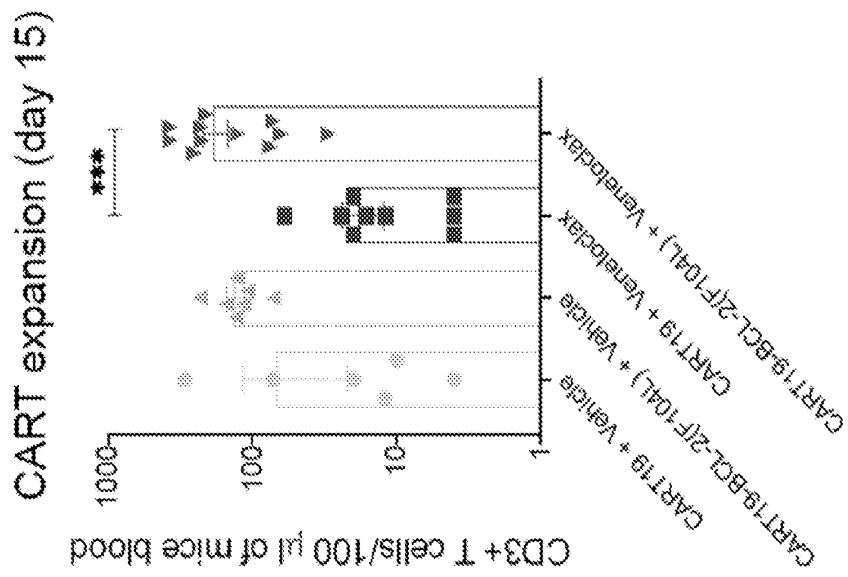


FIG. 12B

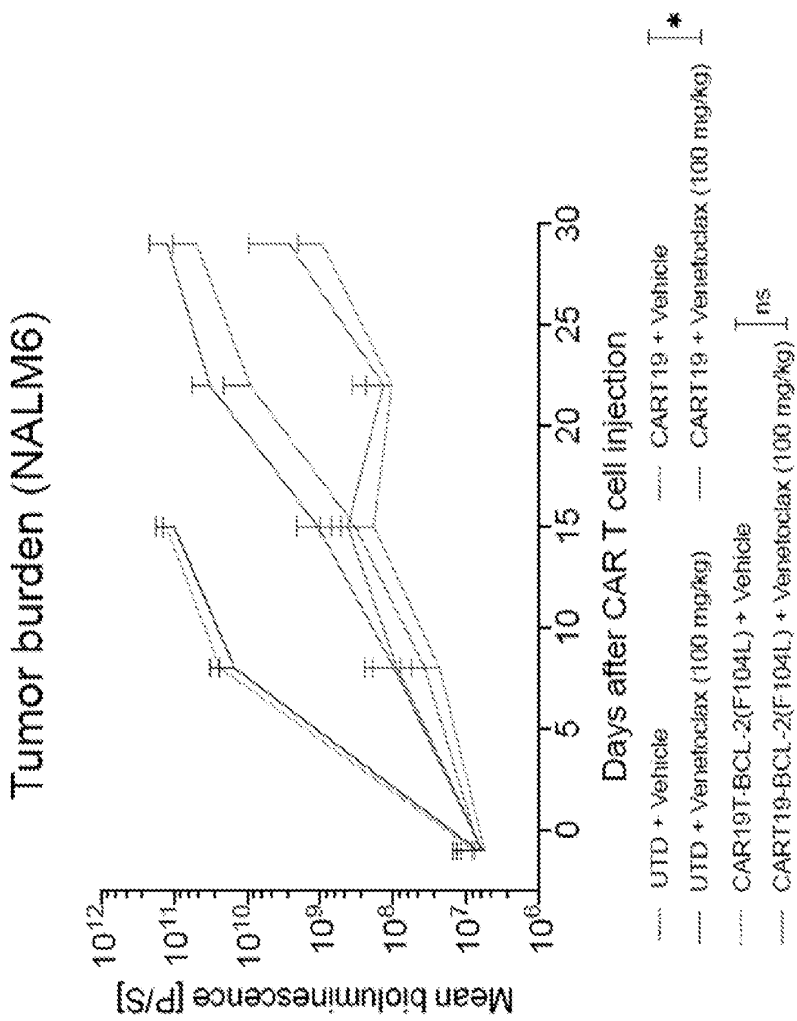


FIG. 12A

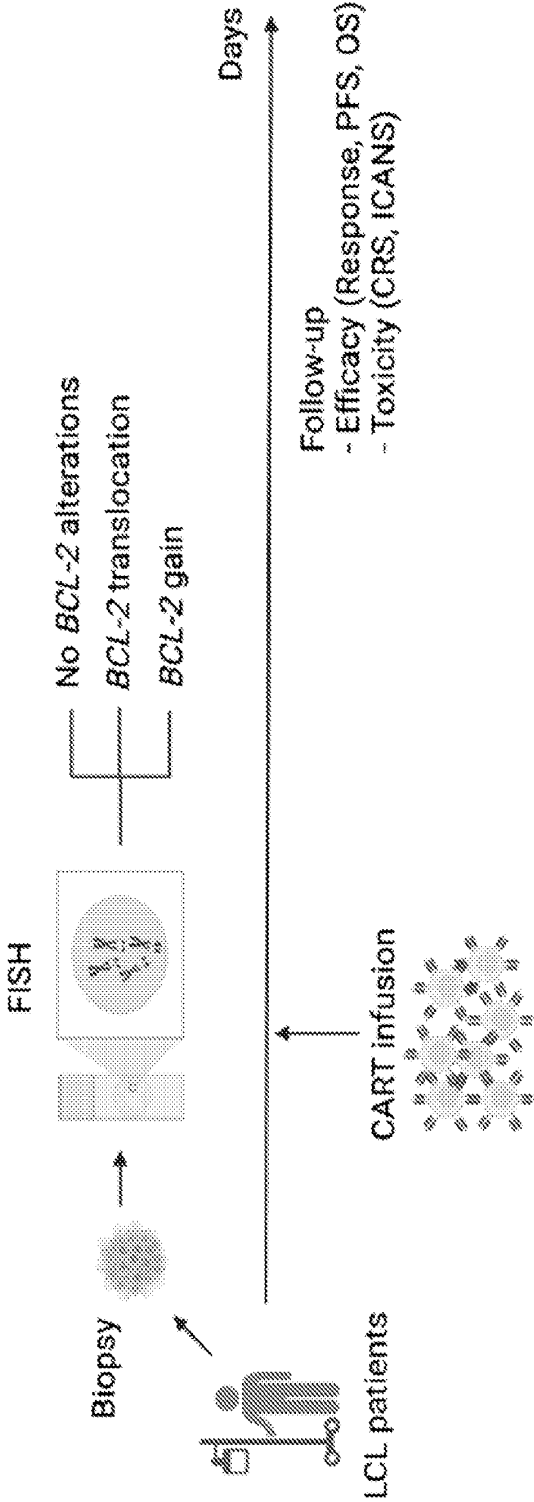


FIG. 13A

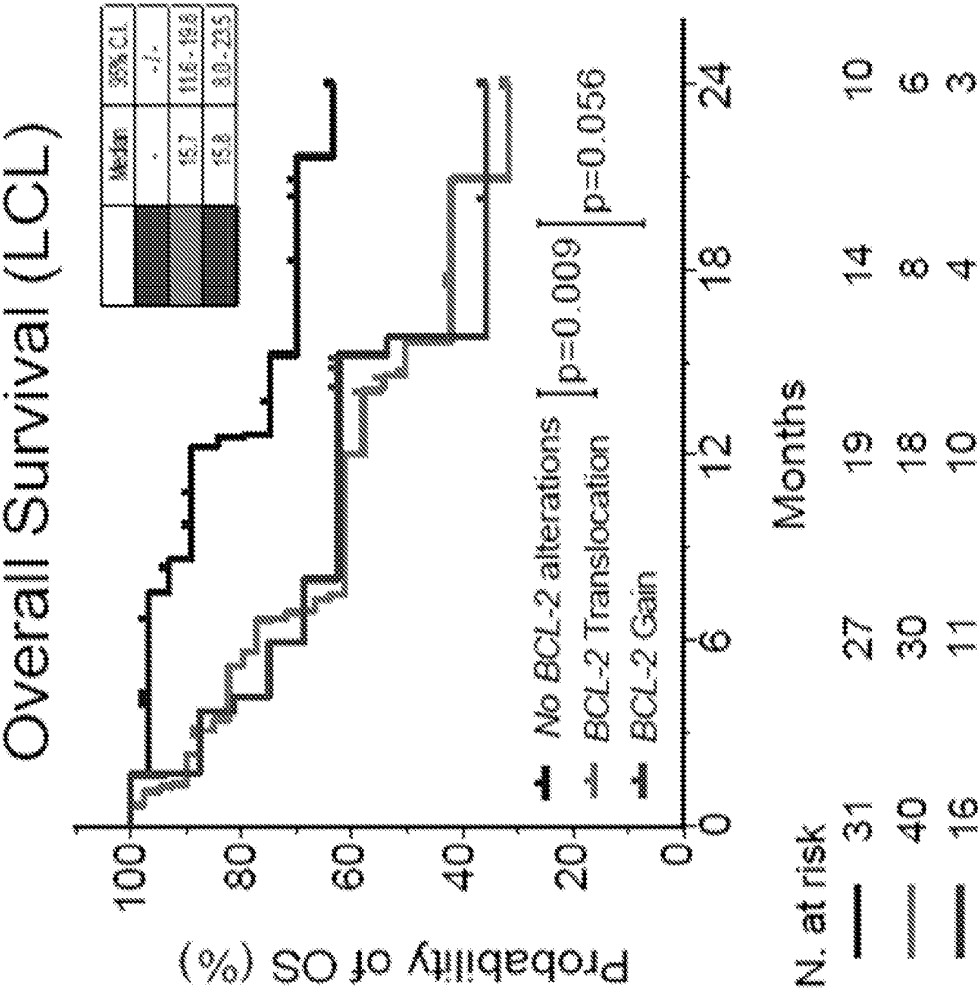


FIG. 13C

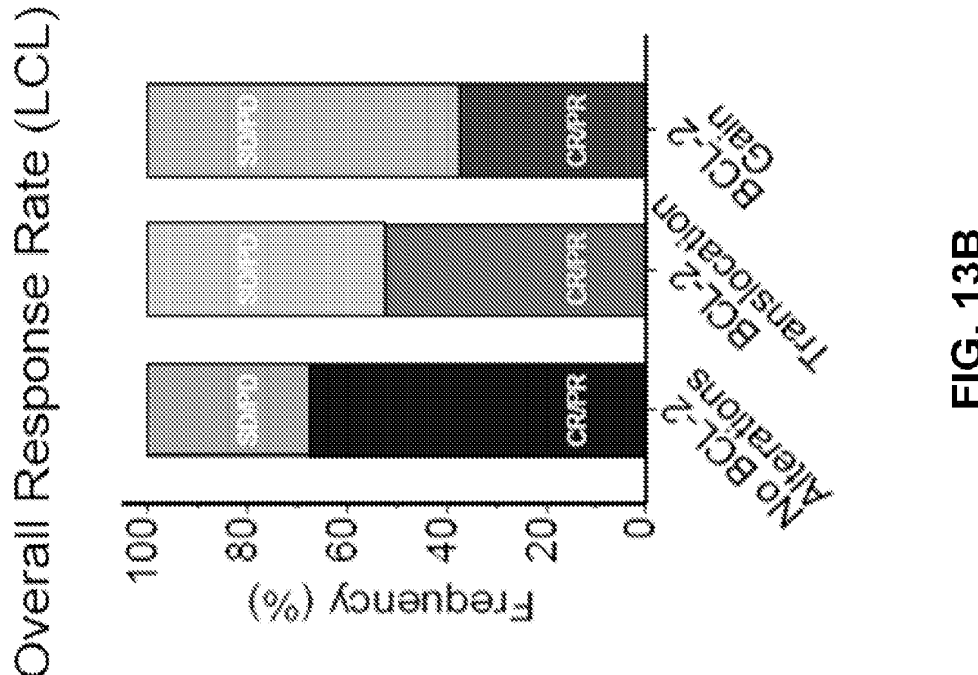


FIG. 13B

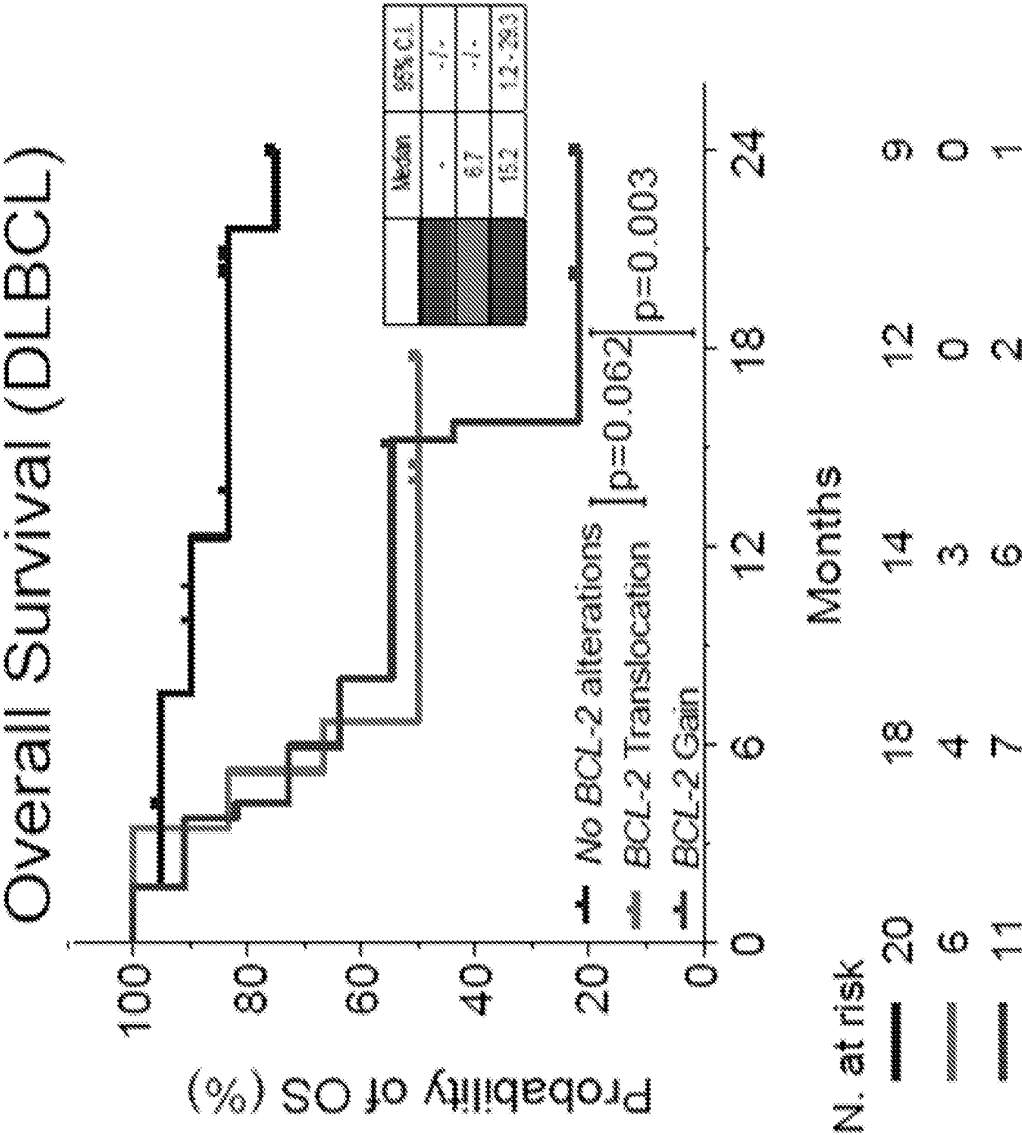


FIG. 13E

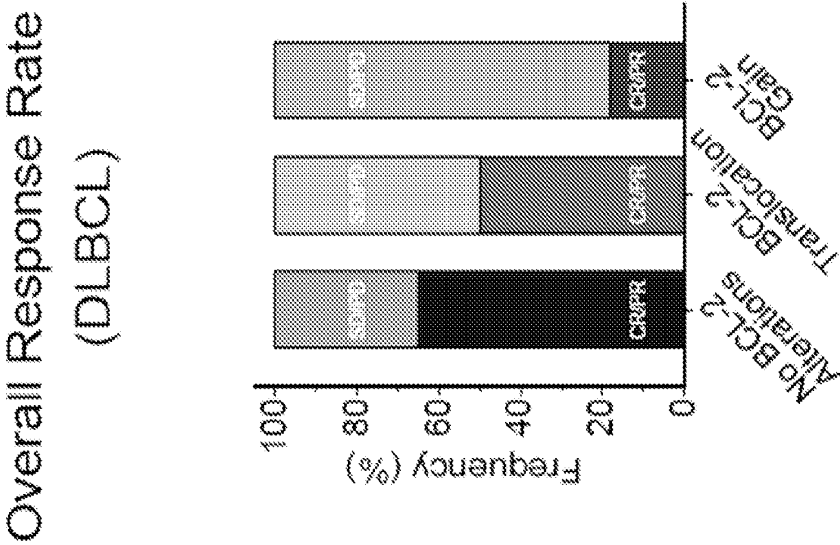


FIG. 13D

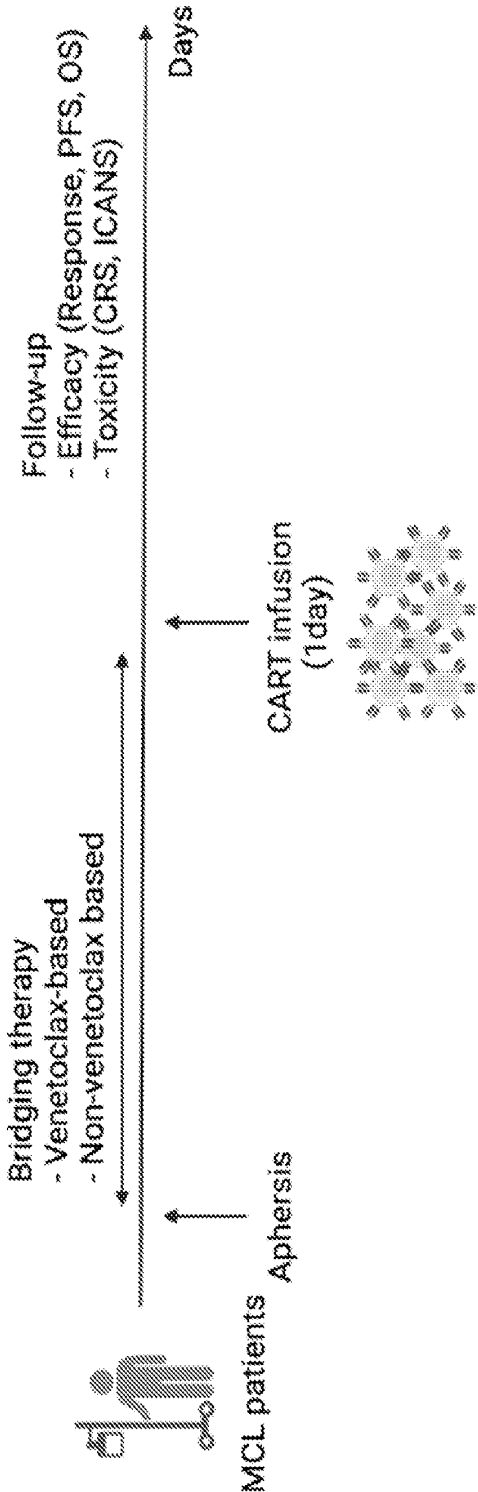


FIG. 13F

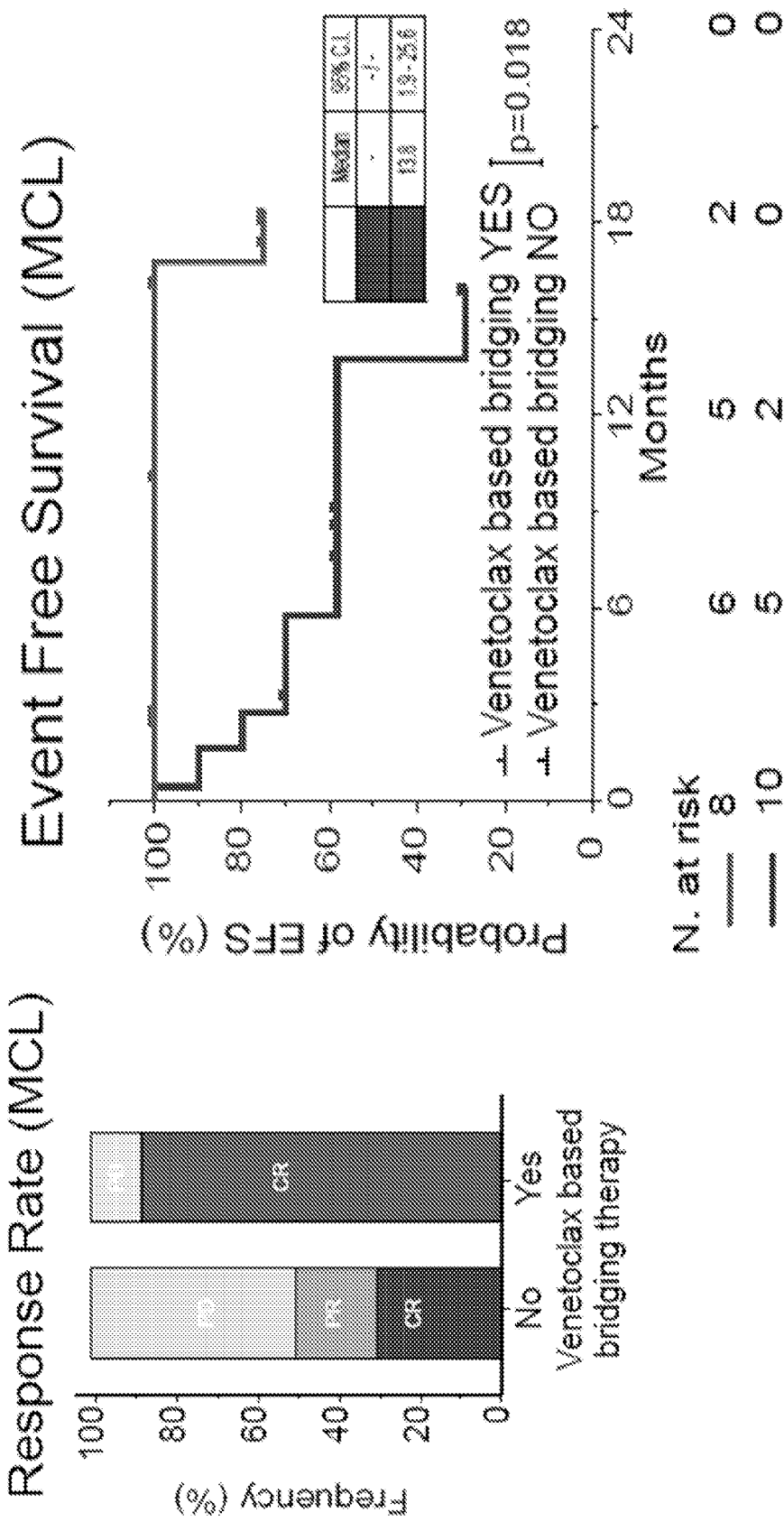


FIG. 13G

FIG. 13H

Characteristic	No BCL-2 alterations n=31 (35.6%)	BCL-2 translocation n=40 (46.0%)	BCL-2 gain n=16 (18.4%)	p
Sex				
Female	15 (48.4%)	9 (22.5%)	8 (50.0%)	0.039
Male	16 (51.6%)	31 (77.5%)	8 (50.0%)	
Age at infusion - years [IQR]	65 [56-70]	68 [58-71]	61 [55-68]	0.200
Diagnosis				
DLBCL NOS	20 (64.5%)	6 (15.0%)	11 (68.8%)	<0.001
HGBCL NOS	2 (6.5%)	0 (0.0%)	2 (12.5%)	
Double hit	4 (12.9%)	16 (40.0%)	0 (0.0%)	
tFL	5 (16.1%)	18 (45.0%)	3 (18.8%)	
Costimulatory domain				
CD28	12 (38.7%)	8 (20.0%)	4 (25.0%)	0.209
4-1BB	19 (61.3%)	32 (80.0%)	12 (75.0%)	
PS ECOG				
0-1	30 (96.8%)	39 (97.5%)	15 (93.8%)	0.783
≥2	1 (3.2%)	1 (2.5%)	1 (6.2%)	
Disease status				
CR	4 (12.9%)	4 (10.0%)	2 (12.5%)	0.921
Persistent disease	27 (87.1%)	36 (90.0%)	14 (87.5%)	

FIG. 14

Progression Free Survival by Disease Subtype

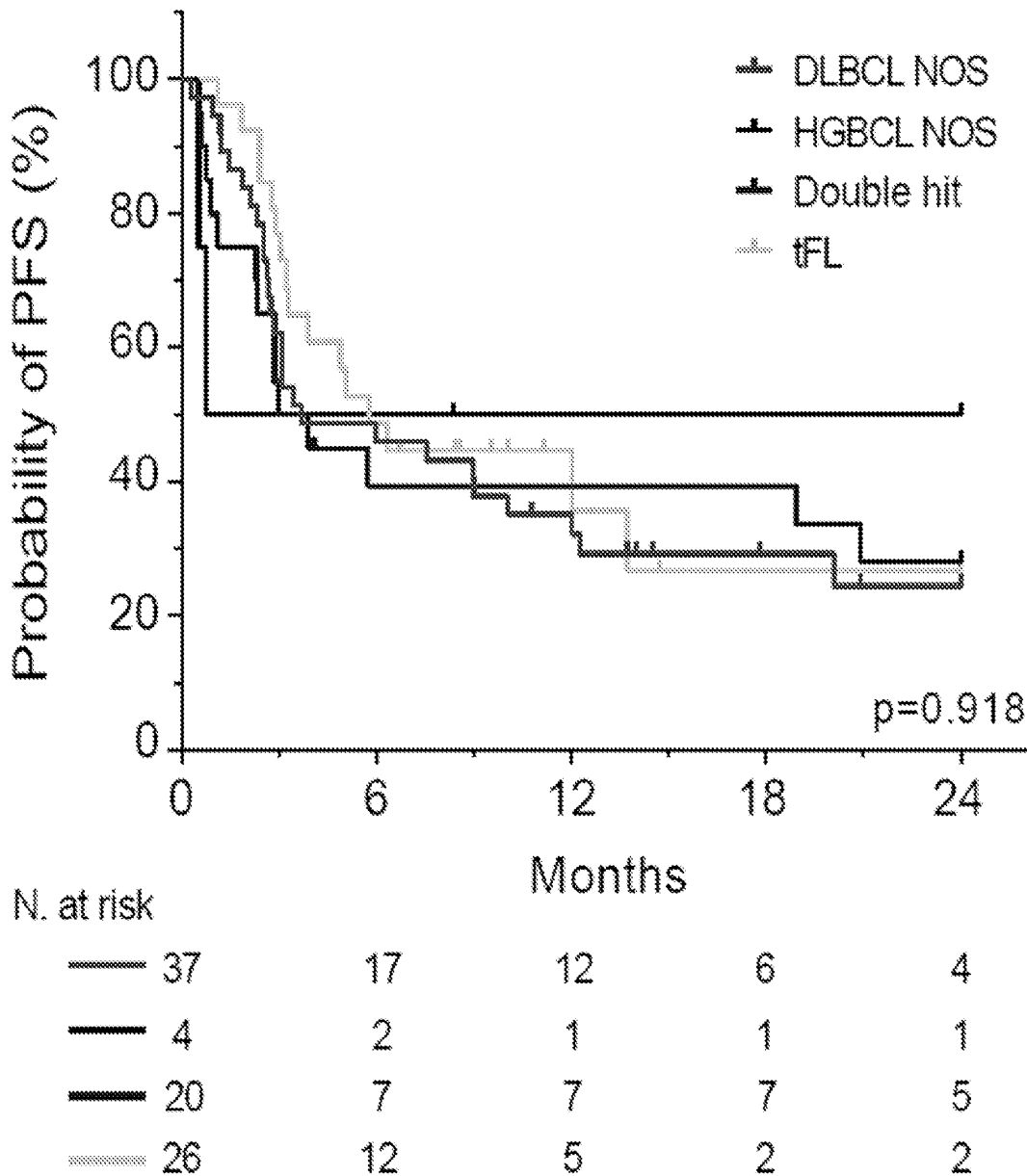


FIG. 15A

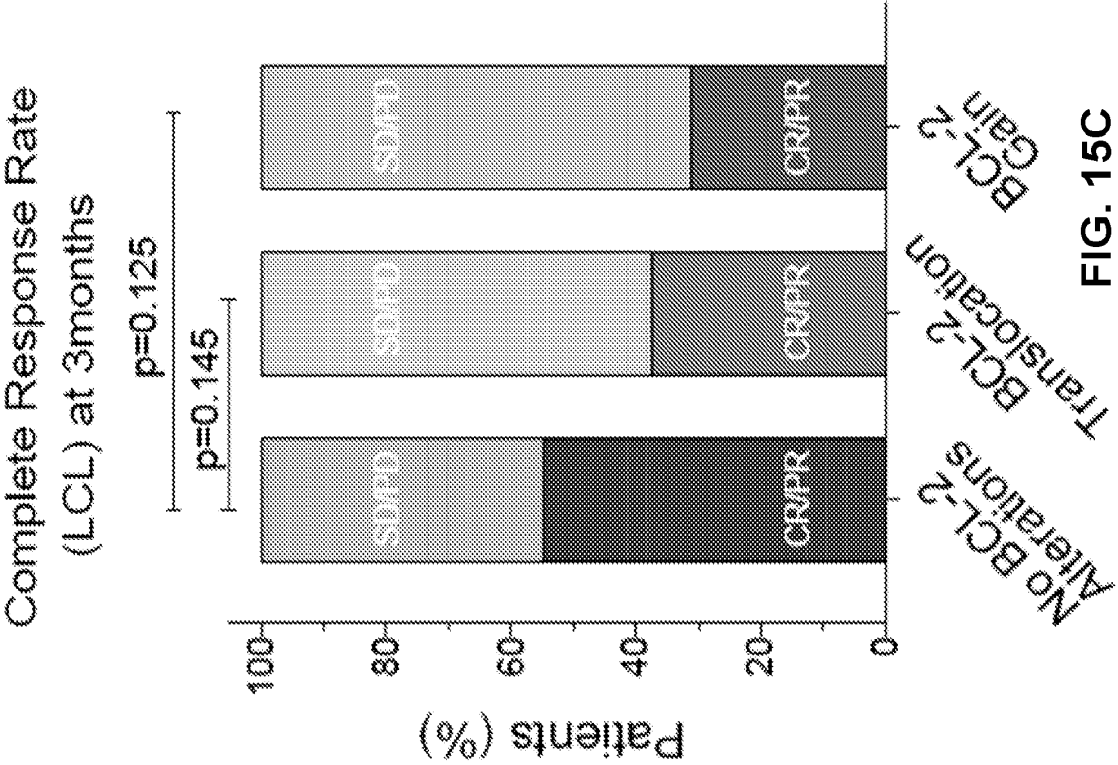


FIG. 15C

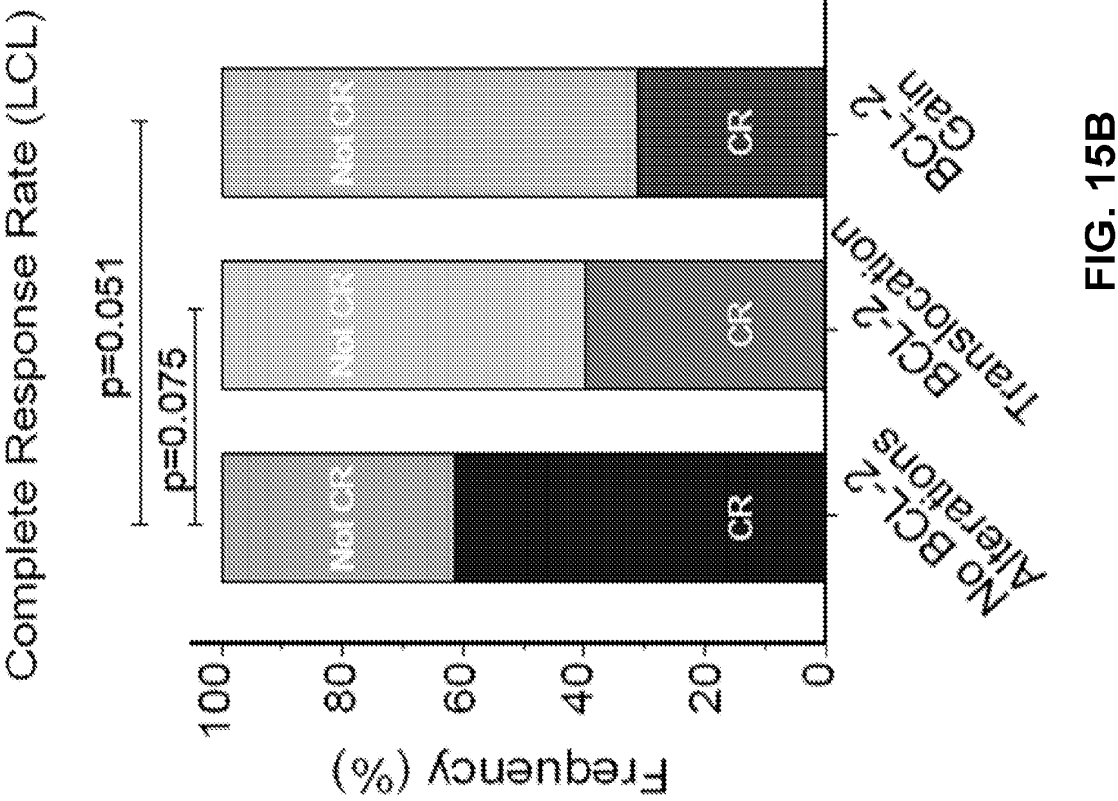


FIG. 15B

Progression Free Survival (LCL)

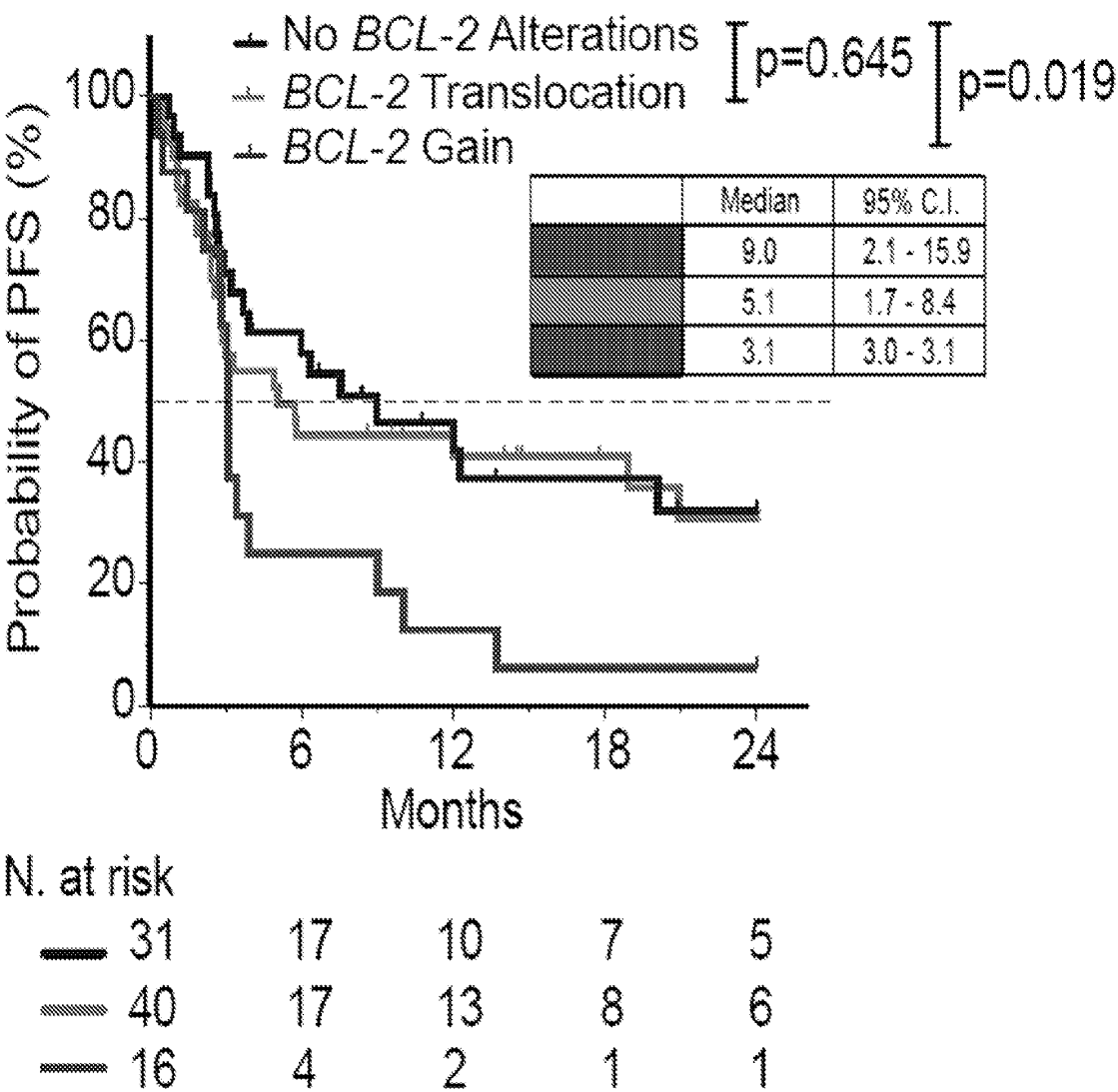


FIG. 15D

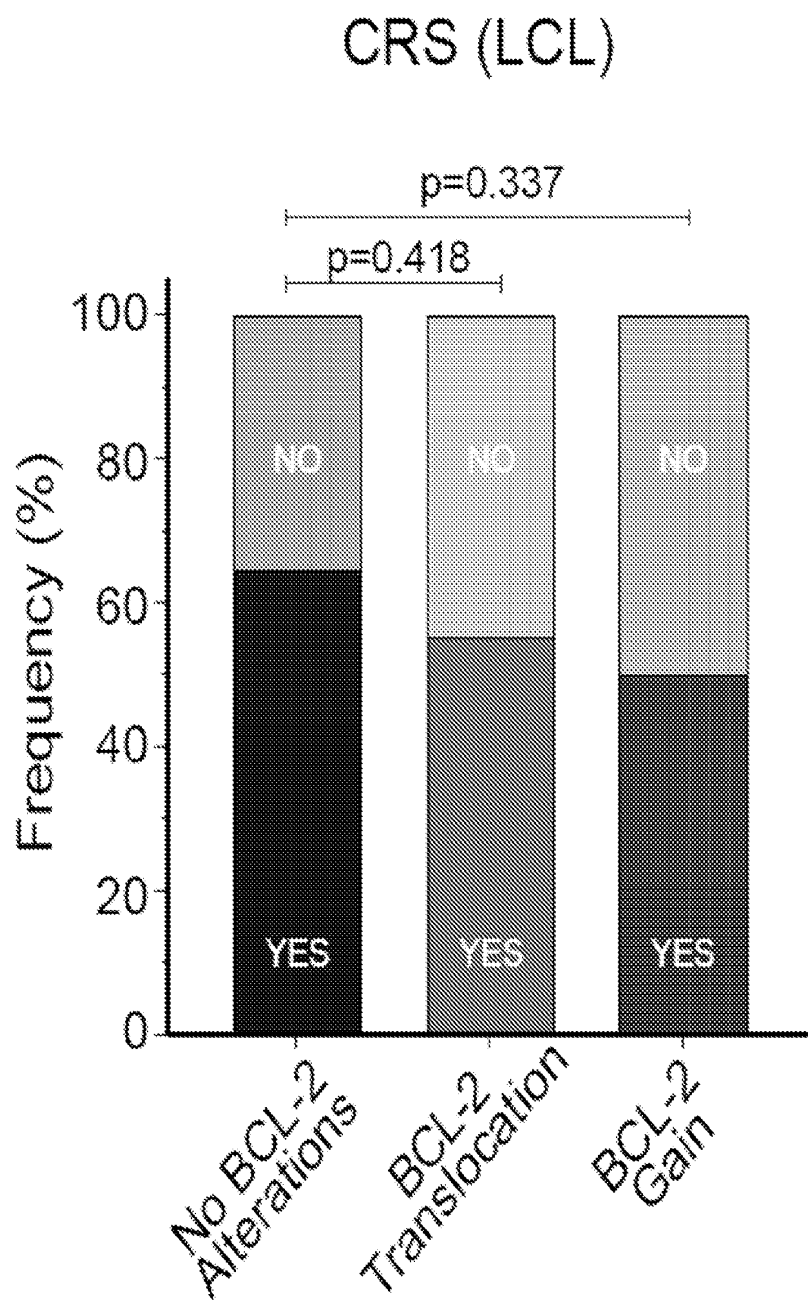


FIG. 15E

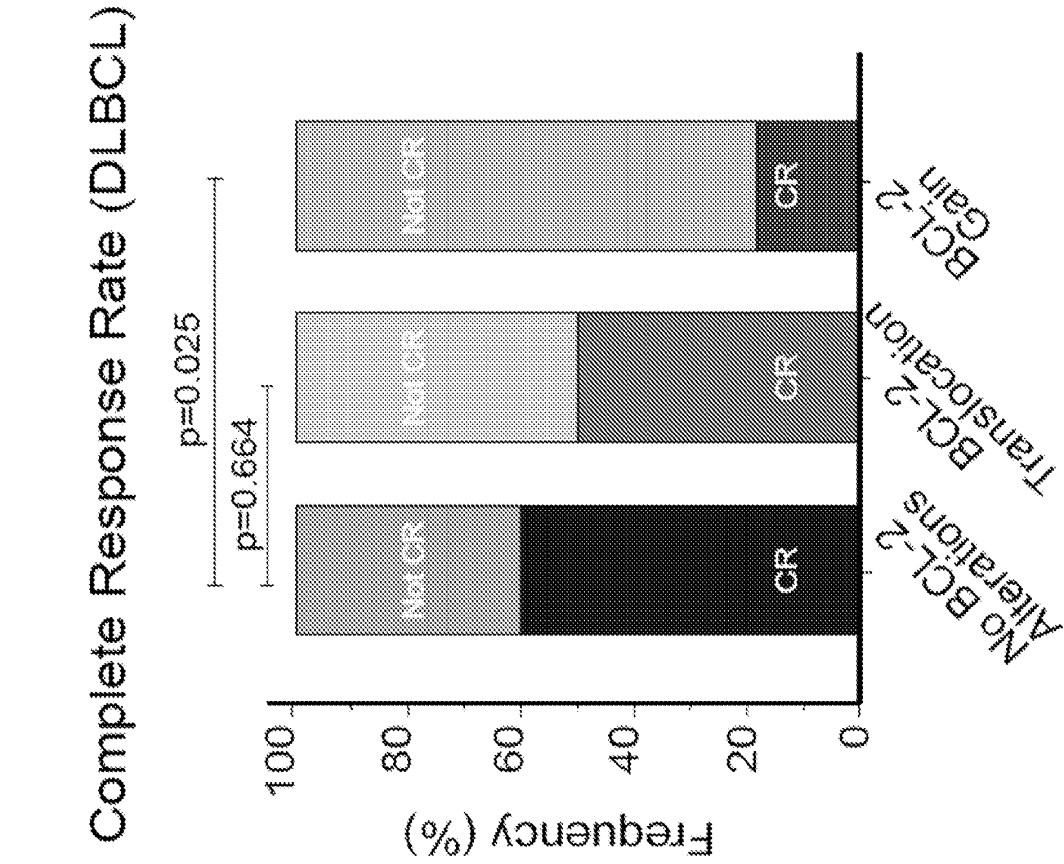


FIG. 15G

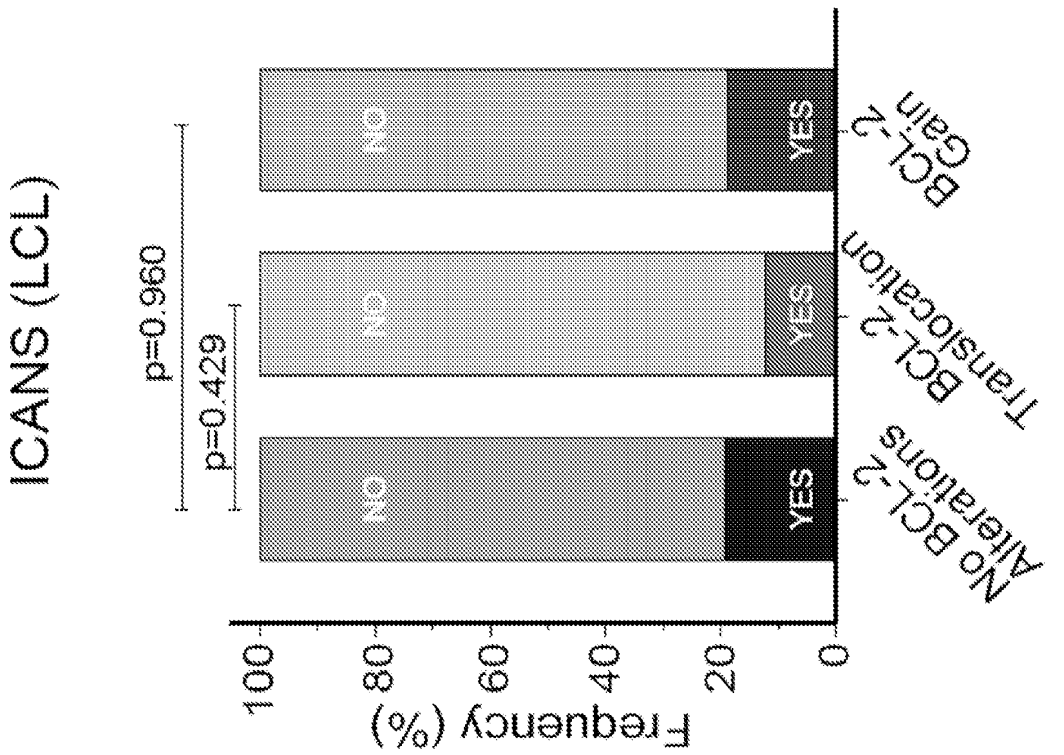


FIG. 15F

Complete Response Rate (DLBCL) at 3months

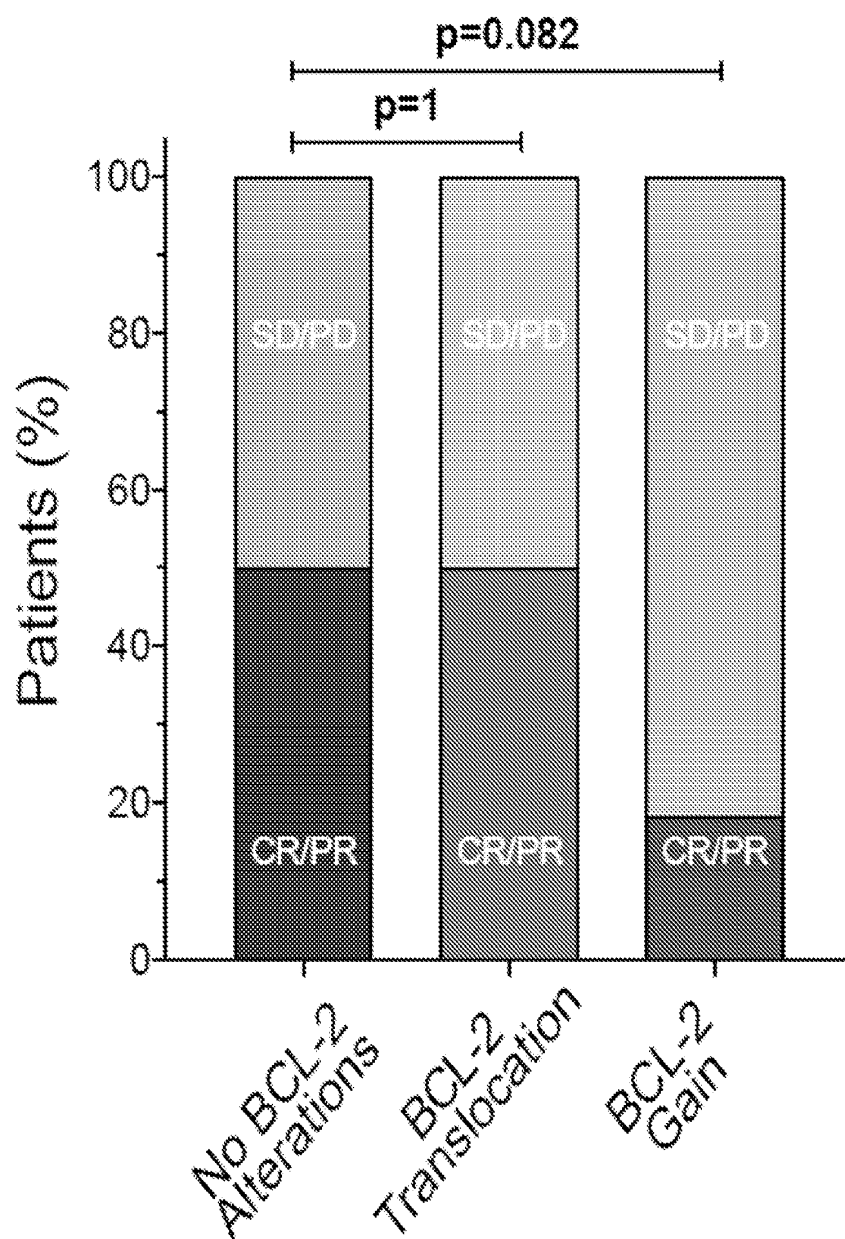
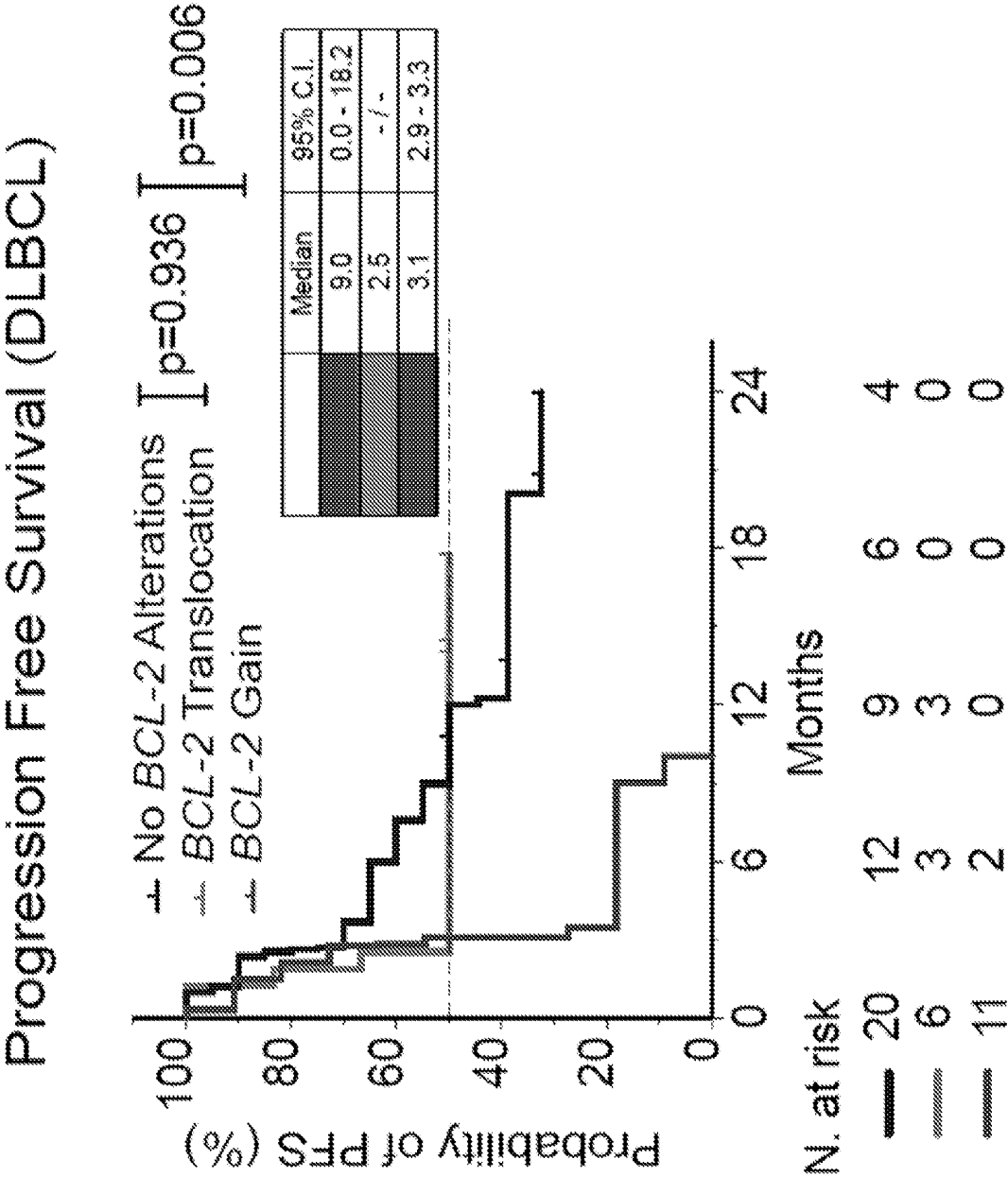


FIG. 15H

FIG. 15I



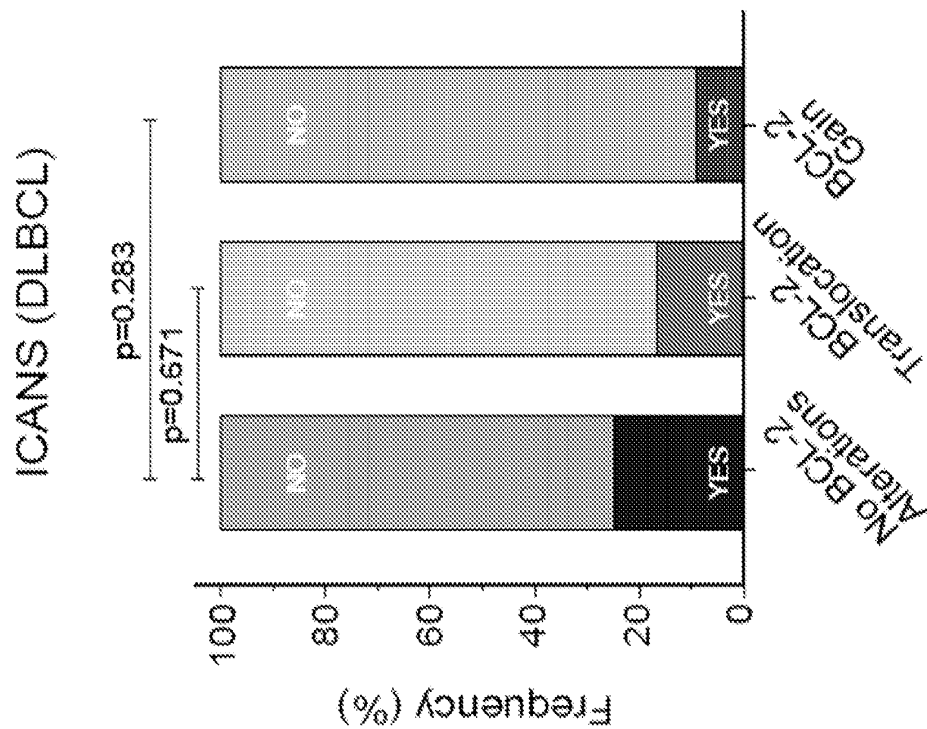


FIG. 15K

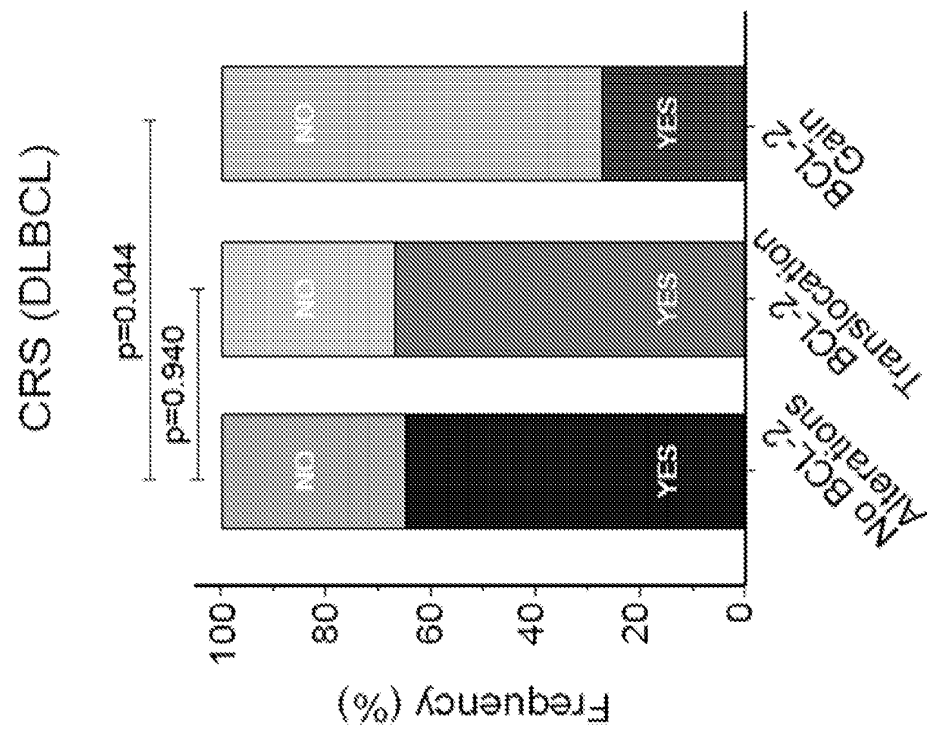


FIG. 15J

FIG. 16

Characteristics	HR	CI (95%)	p
Sex (Male)	1.240	0.705-2.179	0.455
Disease status at infusion (Persistent disease)	2.311	0.814-6.558	0.116
Age at infusion (>65 years)	0.801	0.477-1.345	0.401
BCL-2 gain (Present)	2.077	1.049-4.110	0.036
BCL-2 translocation (Present)	1.125	0.611-2.071	0.706

FIG. 17

Characteristic	No BCL-2 alterations 20 (54.1%)	BCL-2 translocation 6 (16.2%)	BCL-2 gain 11 (27.3%)	p
Sex				
Female	9 (45.0%)	1 (16.7%)	6 (54.5%)	0.313
Male	11 (55.0%)	5 (83.3%)	5 (45.5%)	
Age at infusion - years [IQR]	66 [56-71]	68 [58-72]	62 [57-68]	0.579
Costimulatory domain				
CD28	10 (50.0%)	1 (16.7%)	3 (27.3%)	0.232
4-1BB	10 (50.0%)	5 (83.3%)	8 (72.7%)	
PS ECOG				
0-1	19 (95.0%)	6 (100%)	11 (100%)	0.646
≥2	1 (5.0%)	0 (0%)	0 (0%)	
Disease status				
CR	1 (5.0%)	2 (33.3%)	1 (9.1%)	0.143
Persistent disease	19 (95.0%)	4 (66.7%)	10 (90.9%)	

FIG. 18

Characteristics	HR	CI (95%)	p
Sex (Male)	1.494	0.672-3.324	0.325
Disease status at infusion (Persistent disease)	1.951	0.305-12.477	0.480
Age at infusion (>65 years)	0.697	0.310-1.565	0.381
BCL-2 gain (Present)	2.622	1.077-6.384	0.034
BCL-2 translocation (Present)	1.345	0.278-6.509	0.713

FIG. 19

Characteristics	Total	No venetoclax bridging	Venetoclax bridging	p
	18 (100%)	10 (55.6%)	8 (44.4%)	
Female	4 (22.2%)	1 (10%)	3 (37.5%)	0.163
Age - years	67 [61-73]	67 [62-75]	62 [60-71]	0.188
Previous ASCT	4 (22.2%)	2 (20%)	2 (25%)	0.800
Previous lines of therapies	3 [2-4]	3 [2-4]	3 [2-4]	0.831
ECOG PS ≥1	5 (27.8%)	2 (20%)	3 (37.5%)	0.410
Venetoclax as last therapy (before bridging)	9 (50%)	7 (20%)	7 (87.5%)	0.004

Patient ID	Bridging
MCL1	Acalabrutinib/obinutuzumab/venetoclax
MCL2	No bridging therapy
MCL3	Radiotherapy/venetoclax
MCL4	Ibrutinib/venetoclax
MCL5	Zanubrutinib/Obinutuzumab/venetoclax
MCL6	Radiotherapy
MCL7	Acalabrutinib
MCL8	Acalabrutinib/venetoclax
MCL9	Radiotherapy
MCL10	Acalabrutinib/venetoclax
MCL11	Hyper-fractionated cyclophosphamide
MCL12	Acalabrutinib
MCL13	Acalabrutinib/rituximab
MCL14	Bendamistine/rituximab
MCL15	Ibrutinib/venetoclax
MCL16	Obinotuzumab/venetoclax
MCL17	No bridging therapy
MCL18	Acalabrutinib/obinutuzumab

FIG. 20

In vivo xenograft model to test CART19-BCL-2(WT)

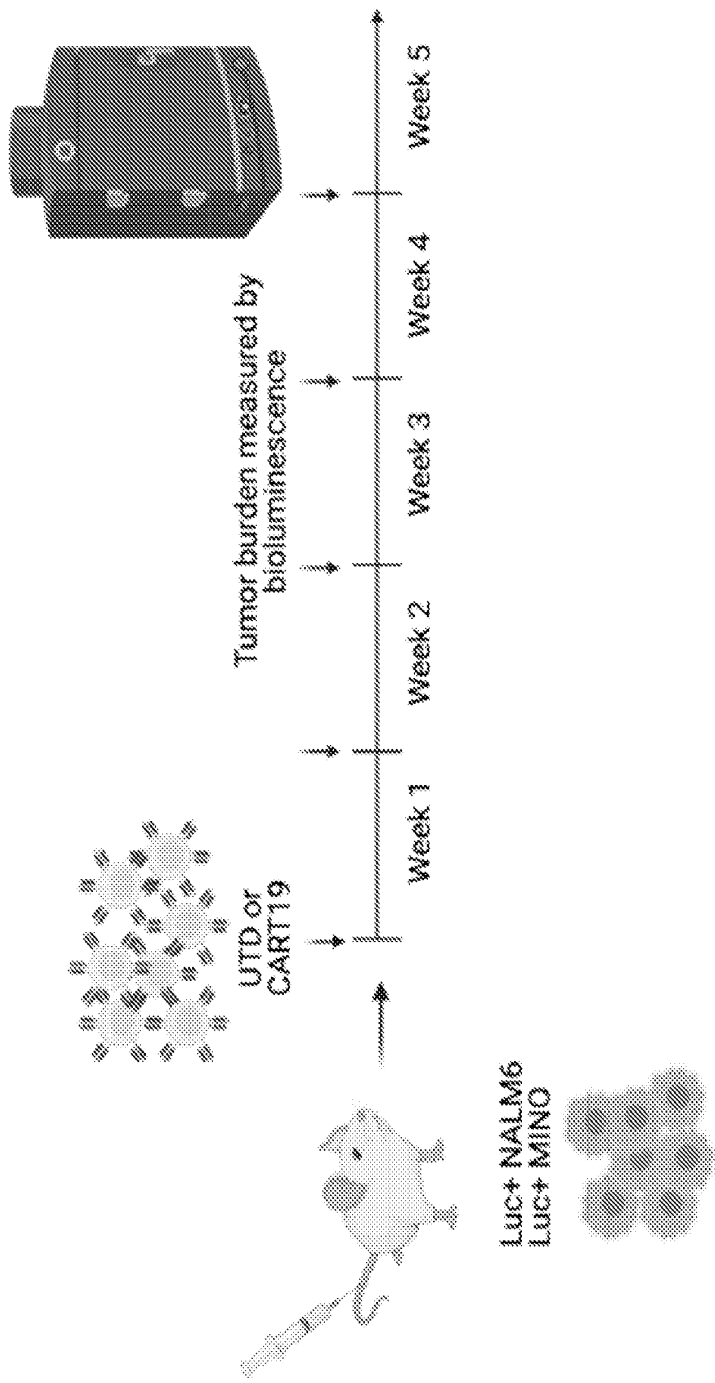


FIG. 21A

Overexpression of BCL-2(WT) enhances CART
anti-tumor efficacy *in vivo* (MINO)

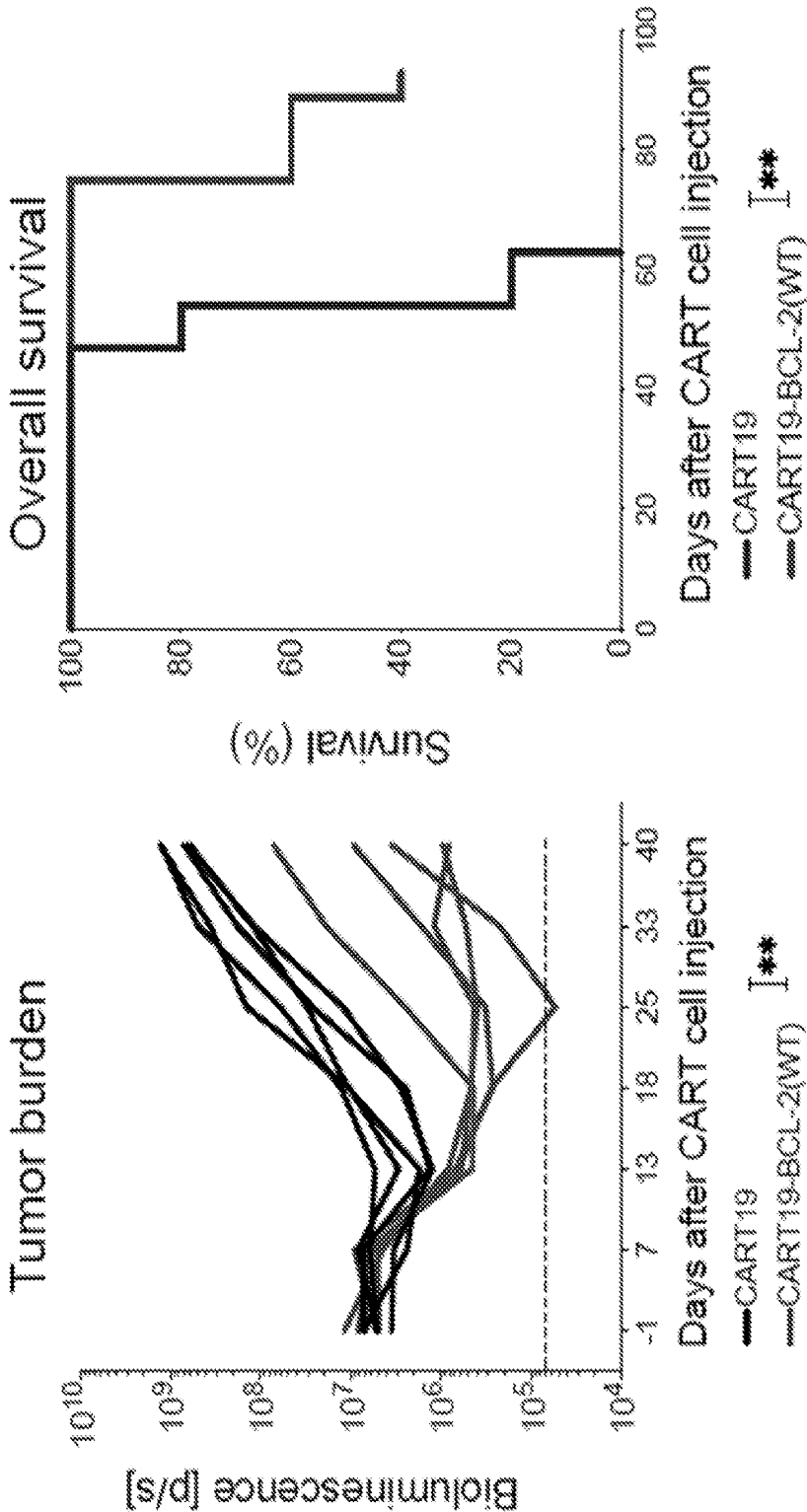


FIG. 21B

Overexpression of BCL-2(WT) enhances
CART anti-tumor efficacy *in vivo* (NALM6)

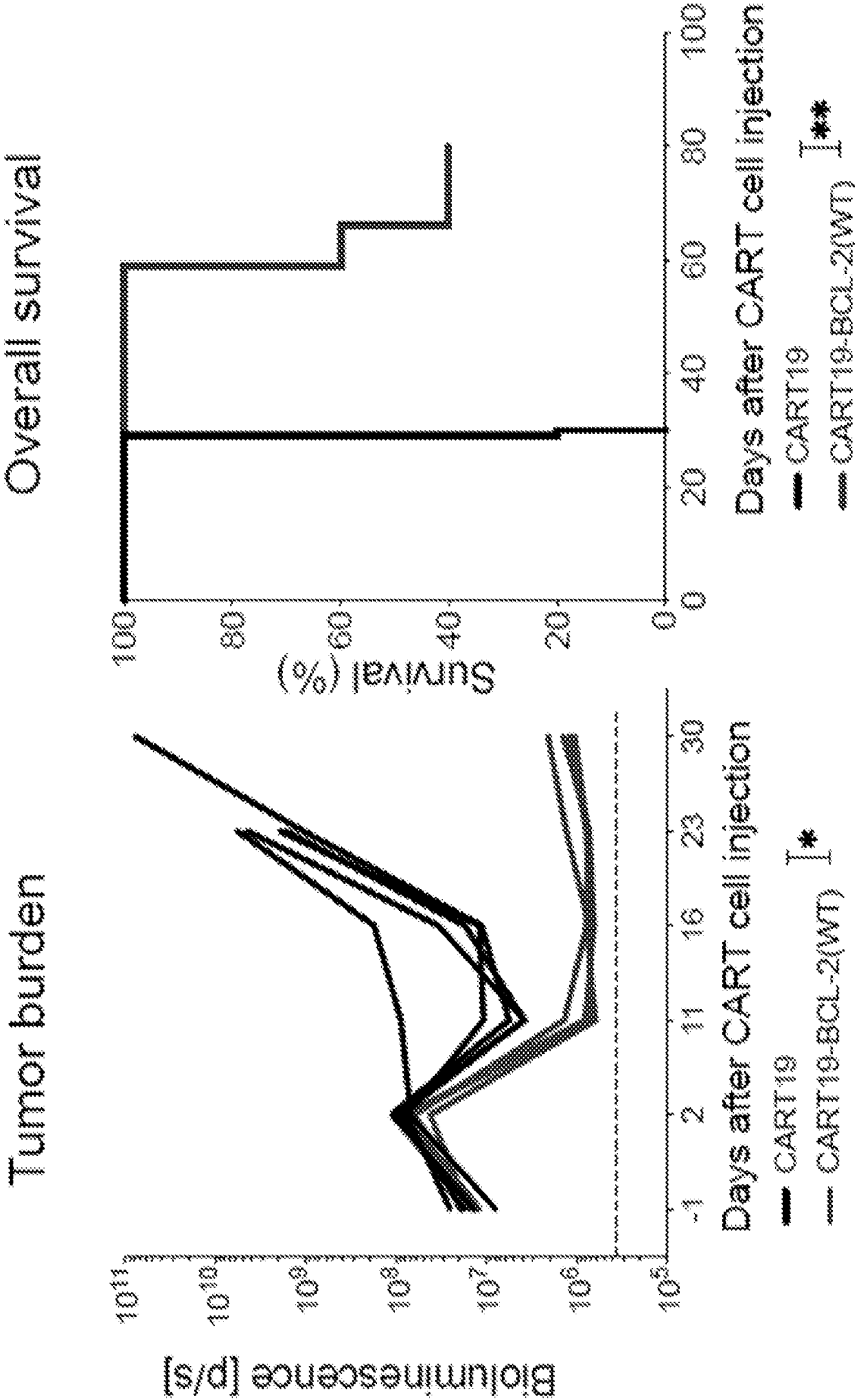


FIG. 21C

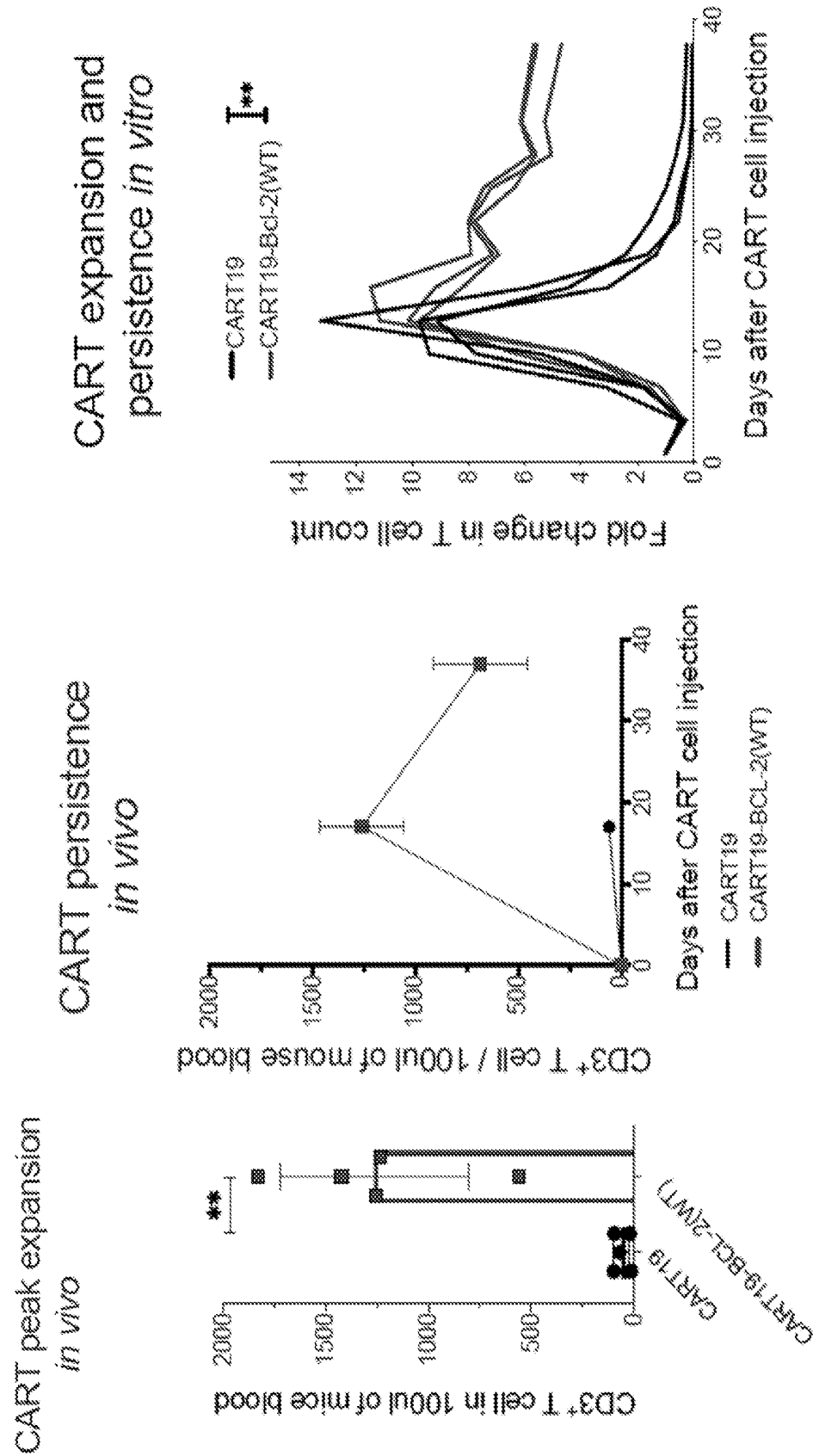


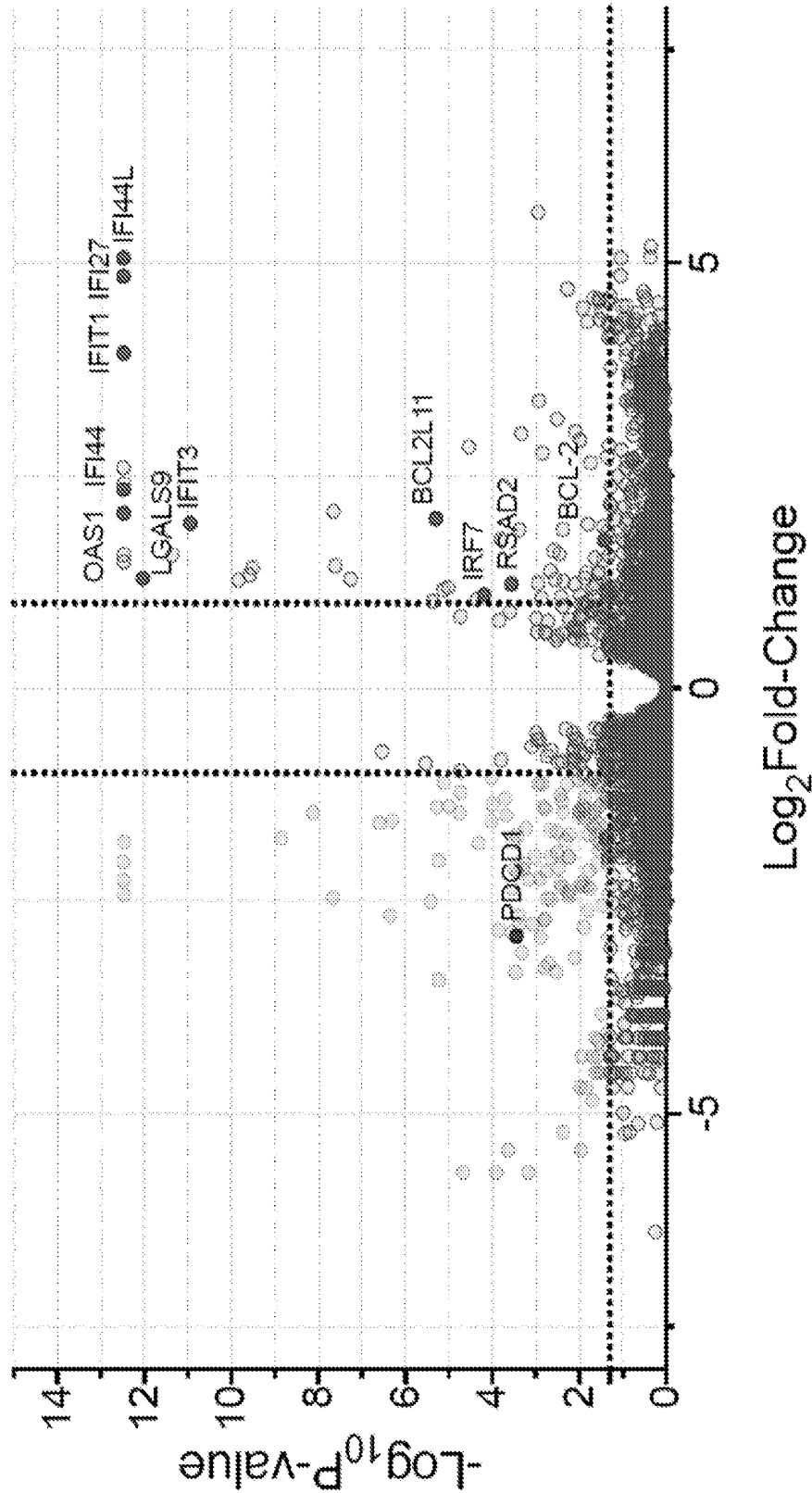
FIG. 21F

FIG. 21E

FIG. 21D

FIG. 21G

Differential gene expression in
CART19-BCL-2(WT) vs CART19



Reduced apoptosis and increased IFN α signaling in CART19-BCL-2(WT)

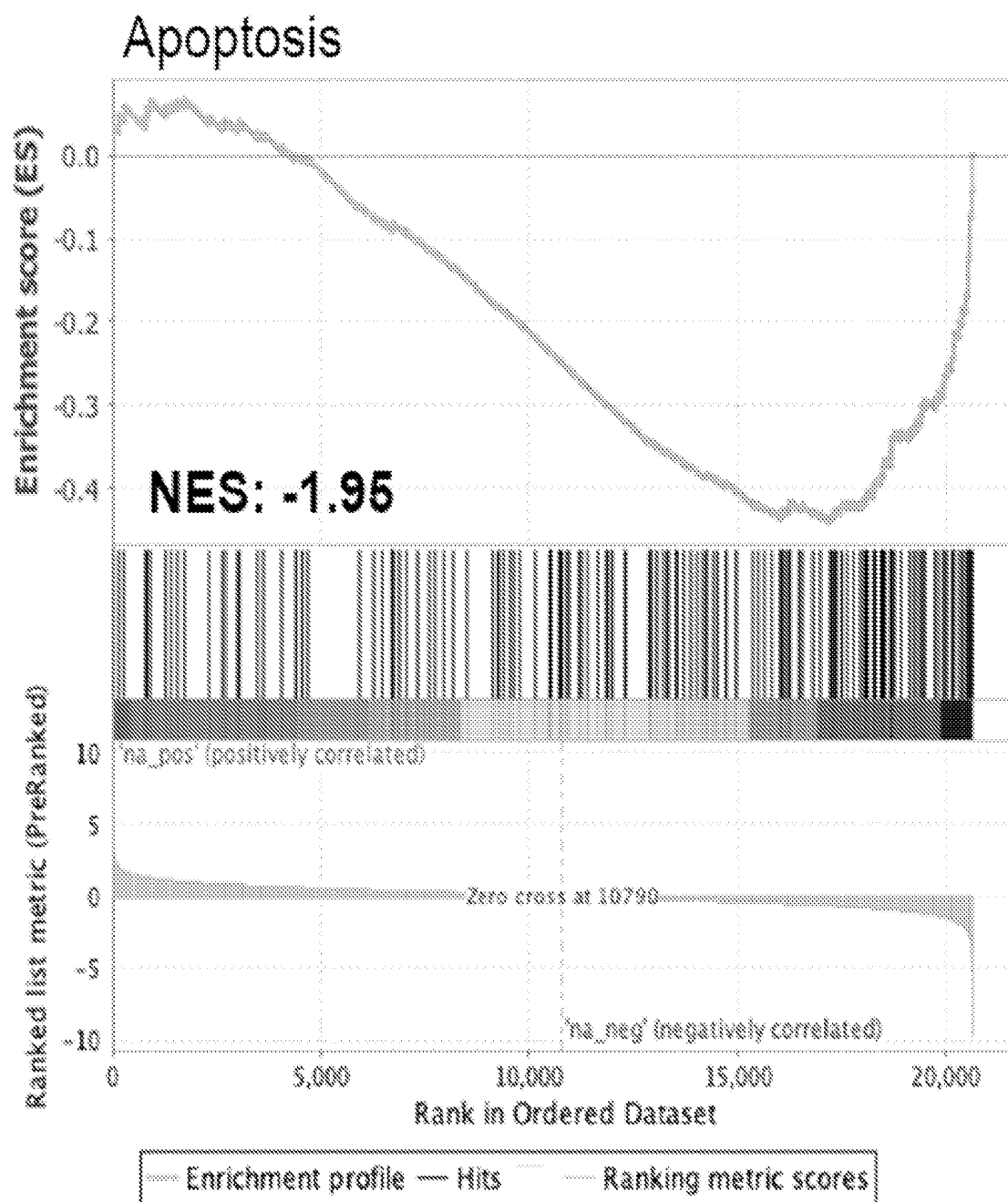


FIG. 21H – 1 of 2

Reduced apoptosis and increased IFN α signaling in CART19-BCL-2(WT)

Interferon Alpha Response

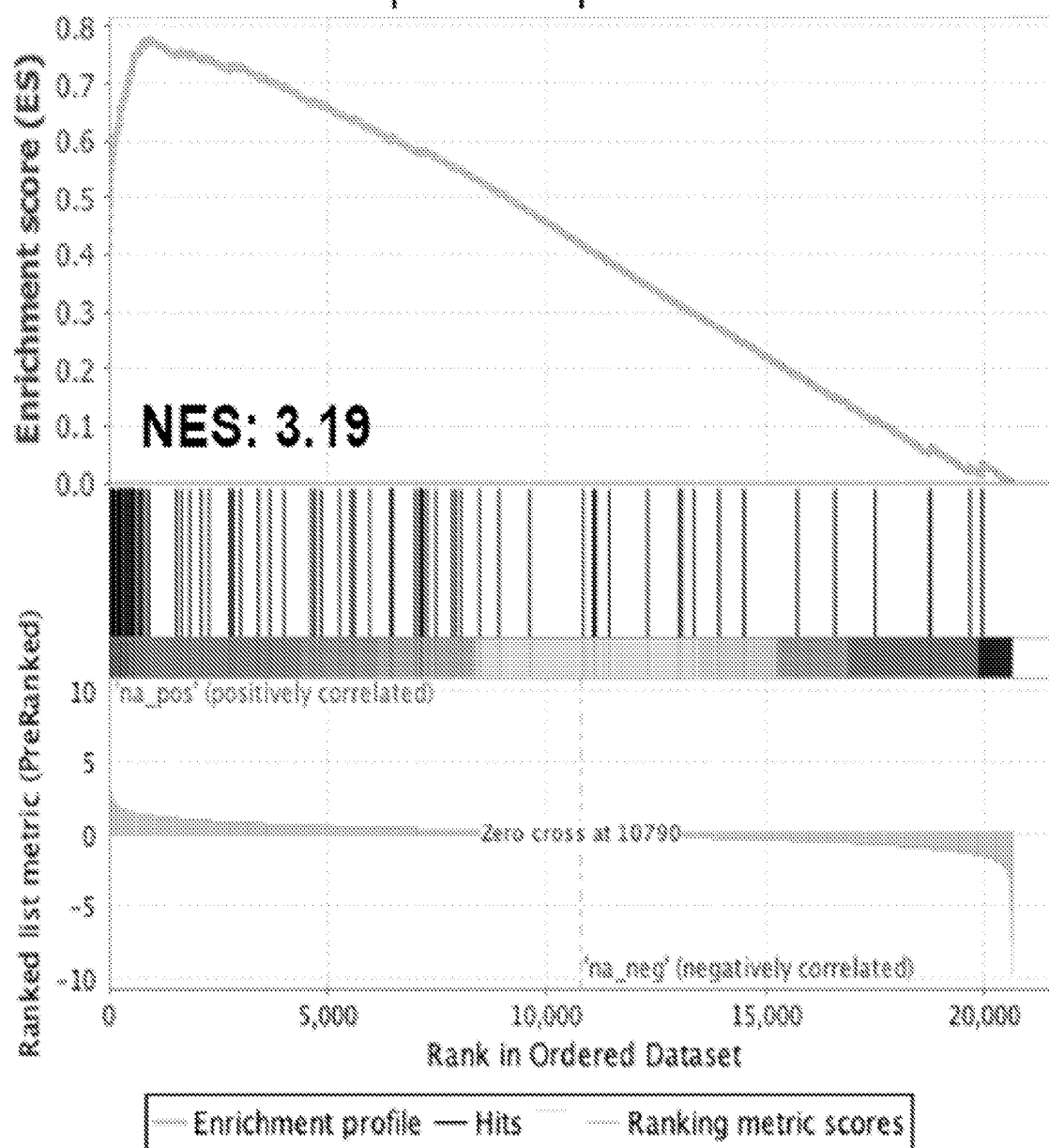


FIG. 21H – 2 of 2

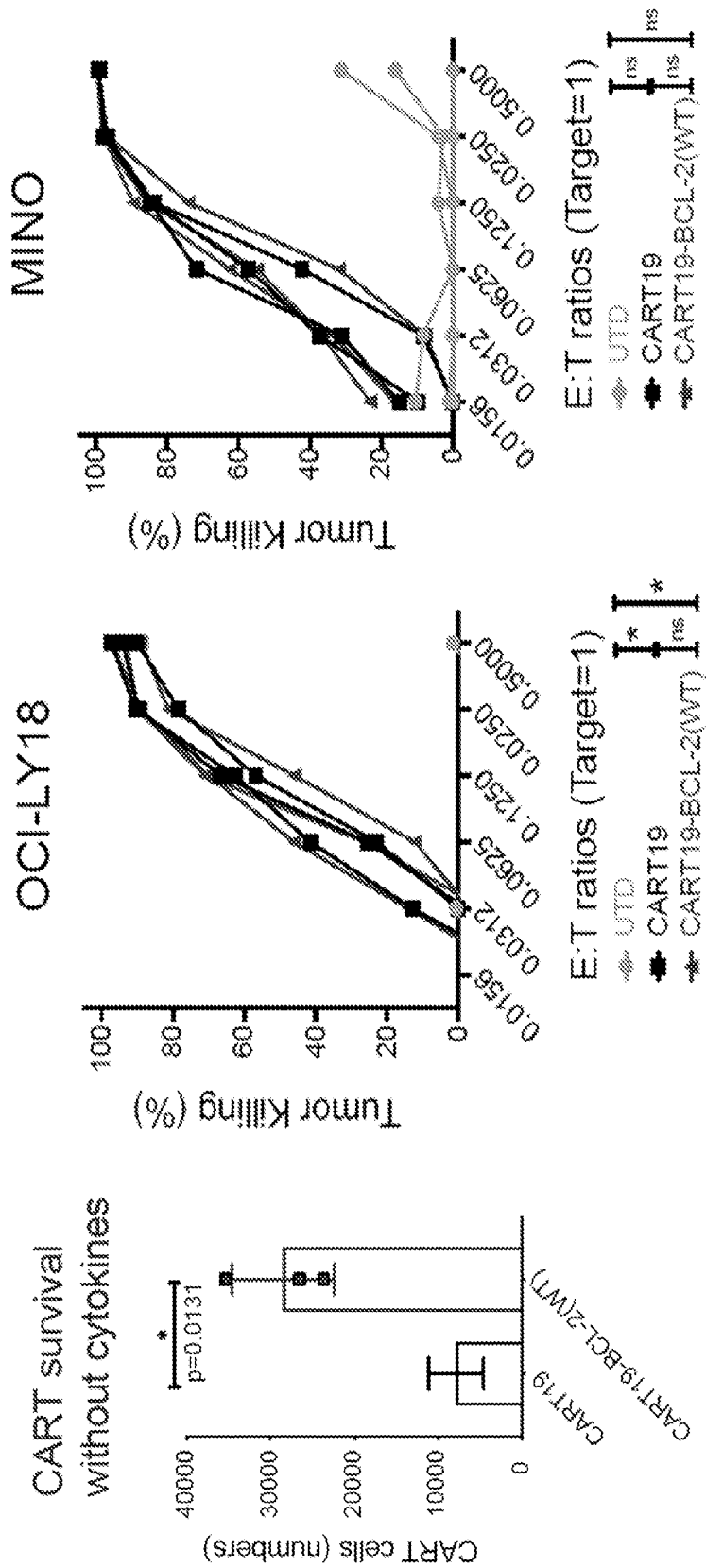


FIG. 21I

FIG. 22A

FIG. 22B

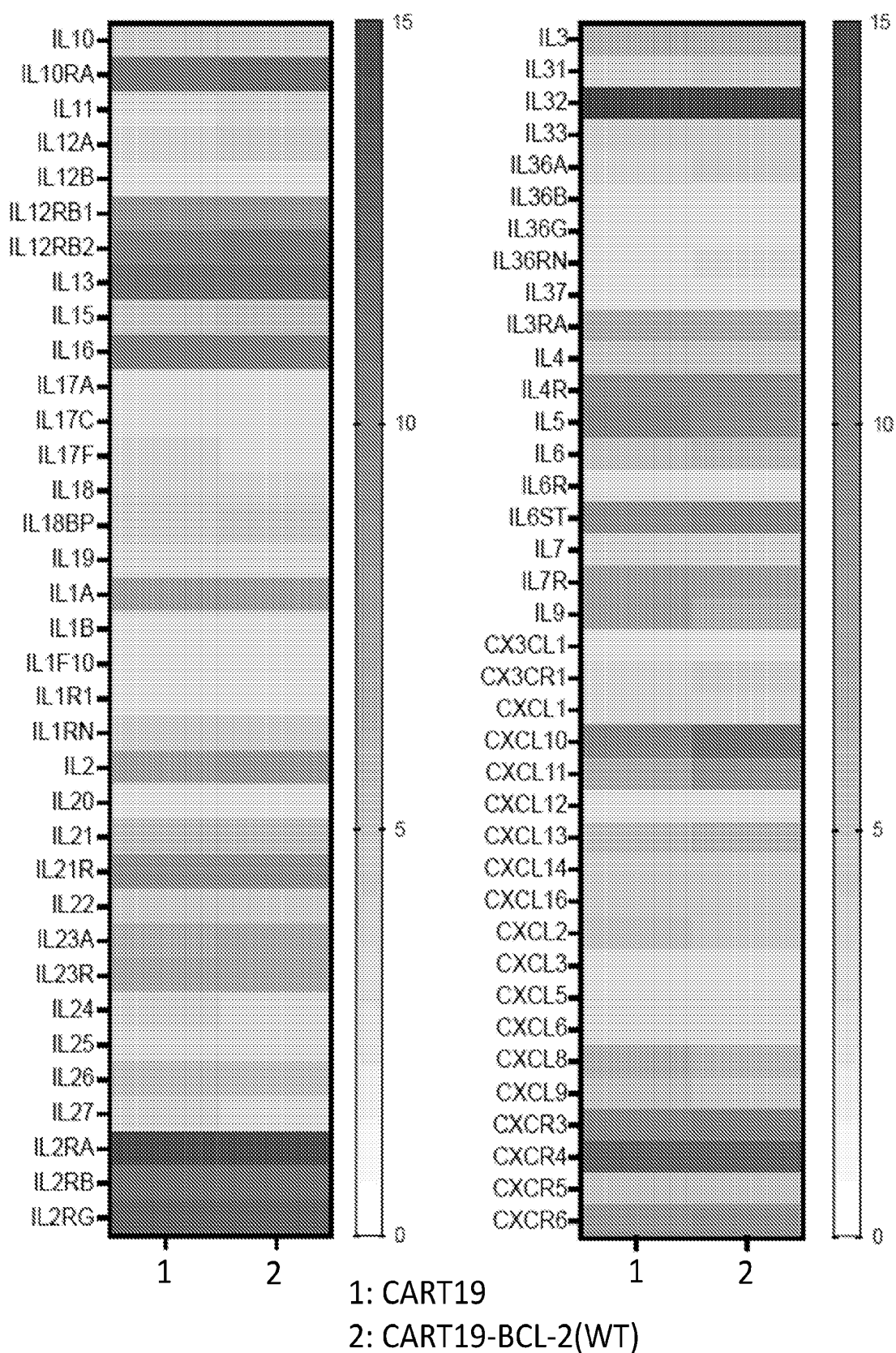
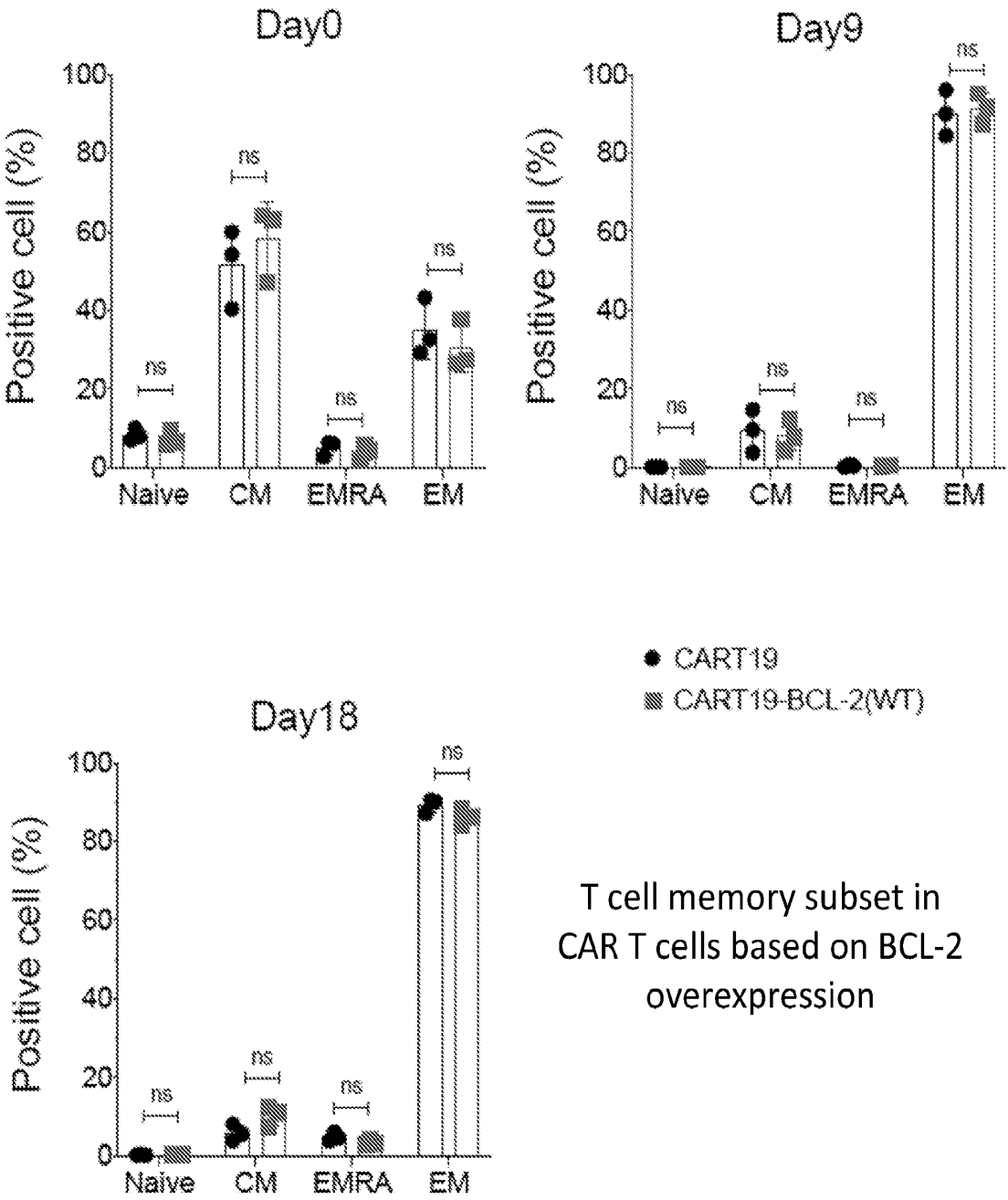


FIG. 22C

FIG. 23



T cell memory subset in
CAR T cells based on BCL-2
overexpression

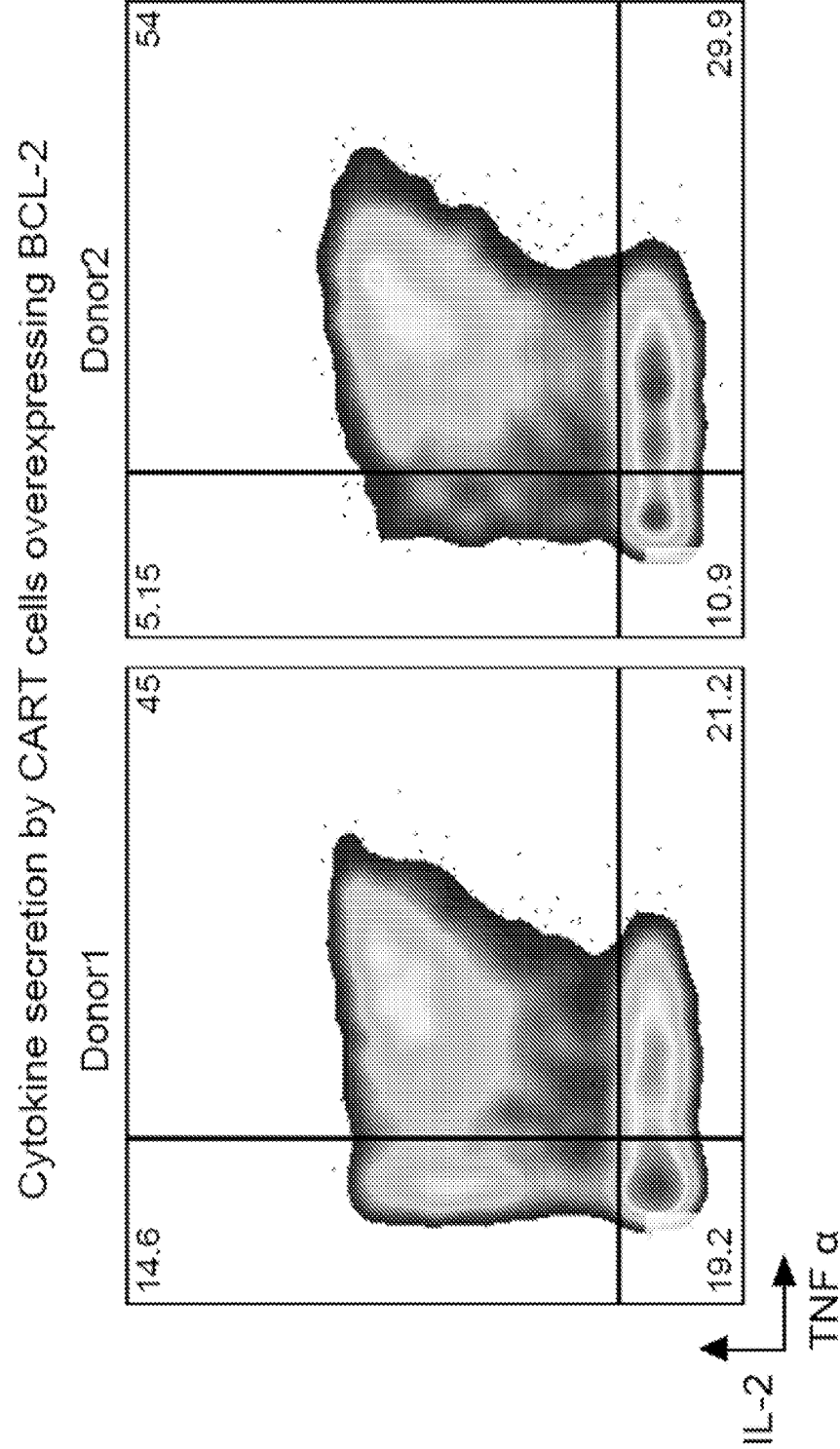


FIG. 24

Gene	Fold change (Log2): Up-regulation	Gene	Fold change (Log2): Down-regulation
RERE	5.05639745	HIVEP3	-14.167773
TLL7	2.05550717	SLC44A5	-2.4243432
GLMN	3.93374699	LOC101930114	-1.8087001
MAN1A2	4.8391148	HSD11B1	-2.0405555
ANXA9	2.5928371	SDCCAG8	-2.2553177
MPZL1	2.39821182	KAZN	-1.7590391
RFWD2	1.48446197	PLEKHM2	-1.4578872
C1orf21	1.56831549	ALDH4A1	-2.4654233
AGRN	2.33350997	EPHA10	-1.5810454
PRKCZ	1.29060914	TRIT1	-0.7457266
ACOT7	1.5637763	LOC107984948	-2.6784297
CAMTA1	1.93889889	ZSWIM5	-1.5625669
PEX14	1.26985622	PIK3R3	-0.8849704
DISP3	1.3296843	EPS15	-2.5069459
DHRS3	1.41325319	PATJ	-1.3995742
EIF4G3	2.08051436	JAK1	-3.428373
KDM1A	1.44084913	PDE4B	-2.0221633
WDTC1	1.28342351	ZZZ3	-1.1133785
ZCCHC11	1.02319973	MCOLN2	-1.3860676
DAB1	1.99265327	COL24A1	-1.2221375
ST8GALNAC3	1.15689894	HS2ST1	-0.9748301
IFI44L	1.18646723	LOC105378842	-1.4637131
CCDC18-AS1	0.8408036	DPYD	-5.6933743
CEPT1	2.83427752	LOC100996724	-1.8212558
ATP1A1	1.04119102	PDE4DIP	-1.5538288
RNF115	1.09921967	OTUD7B	-1.0498492
UHMK1	0.79693429	NUP210L	-1.3637281
ALDH9A1	1.75145281	MUC1	-5.6695715
CACNA1E	0.89683141	PMF1	-2.8410451

FIG. 25 – 1 of 5

SMG7	1.22254592	SCYL3	-0.841737
LYPLAL1-AS1	1.85962744	DNM3	-1.2986921
RAB3GAP2	2.99169545	SOAT1	-1.4907108
LOC100996442	0.8160047	ACBD6	-5.4316107
TTL10	0.66098881	ASPM	-2.8667908
PUSL1	1.23730928	NEK7	-2.3482955
VWA1	5.59354572	PPP1R12B	-1.8125307
CDK11A	3.37843841	PIK3C2B	-3.3371433
MMEL1	1.05651742	CDK18	-2.1256231
MEGF6	2.75865664	RASSF5	-2.9123348
CHD5	0.65782699	CR1	-1.73241
UTS2	0.64601938	KCNH1	-2.1693471
PIK3CD	0.78880117	LPGAT1	-2.6801073
UBE4B	1.38201431	FLVCR1	-2.7825965
MTHFR	1.61740401	SUSD4	-3.1051379
TNFRSF1B	1.27837059	WDR26	-2.1299614
LOC105376767	0.5618423	URE2	-2.0609054
LOC107985735	3.162861	COG2	-1.6419901
SZRD1	0.61197176	DISC1	-5.6976205
SDHB	1.57943901	LOC105373262	-2.2458444
AKR7L	1.06878088	KIF26B	-0.6847604
LOC105376819	0.63763723	SMYD3	-2.777396
UBXN10-AS1	0.96303021	LOC105373277	-1.985293
VWA5B1	1.86506605	LOC105378580	-0.5238177
USP48	1.25737917	LOC100287934	-0.6054065
HNRNPR	4.68805657	SSU72	-1.1196677
RCAN3	0.80451526	GNB1	-0.6066699
MAN1C1	0.70745486	MORN1	-2.238997
AIM1L	0.69969097	PLCH2	-2.921489
HMGN2	1.22217557	TTC34	-1.1178717
ARID1A	0.58320175	TP73	-2.7296469

FIG. 25 – 2 of 5

Gene	Fold change (Log2): Down-regulation	Gene	Fold change (Log2): Down-regulation
NPHP4	-1.3920928	MACF1	-0.7660559
KCNAB2	-3.2809908	LOC105378672	-4.6955557
NOL9	-2.7126525	SCMH1	-2.6131126
DNAJC11	-1.4219246	FOXJ3	-2.3190543
MIR34AHG	-2.1523978	CCDC30	-1.7200811
SPSB1	-0.7968814	LOC339539	-2.1470772
SLC25A33	-2.4704553	MED8	-1.1434513
NMNAT1	-3.228294	ST3GAL3	-2.3554038
KIF1B	-1.986875	C1orf228	-0.6770053
CASZ1	-1.6737105	LOC105378690	-4.8439673
MTOR	-0.7322247	EIF2B3	-1.0742536
FBXO6	-2.4833901	TESK2	-4.3254576
VPS13D	-1.6934467	NASP	-1.596338
PRDM2	-3.3319954	FAAH	-1.0578746
SPEN	-1.9274856	SPATA6	-1.4530694
FBXO42	-0.8717861	BEND5	-1.6417057
MST1P2	-2.1122285	OSBPL9	-4.103402
RCC2	-2.287404	TXNDC12	-0.4725874
UBR4	-1.2537123	ZFYVE9	-4.5202743
CAPZB	-2.3357799	COA7	-1.4221776
TMCO4	-0.8640736	C1orf123	-1.7571103
UBXN10	-1.3197539	YIPF1	-2.0692042
ECE1	-1.4626684	SSBP3	-0.6934732
RAP1GAP	-5.2211388	TTC22	-1.1429803
HSPG2	-1.7883458	LINC01135	-4.3253203
LOC105376845	-0.478869	LOC107984961	-4.1458461
ASAP3	-1.1301176	FGGY	-4.5086523
LOC107984928	-1.9859718	NFIA	-1.5859067
FUCA1	-2.4113524	LOC107984965	-1.9121632

FIG. 25 – 3 of 5

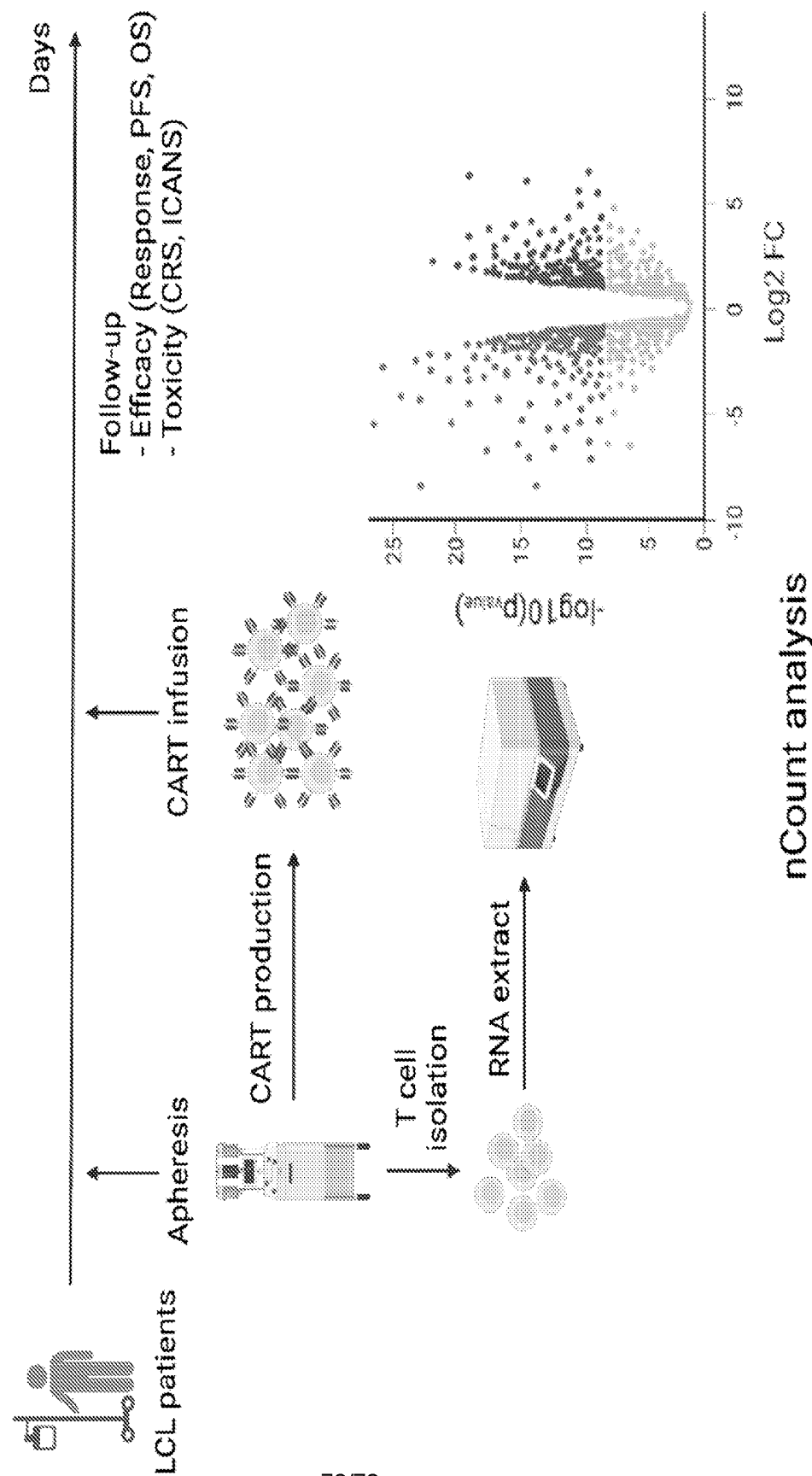
STPG1	-1.9776106	EFCAB7	-1.1096414
CLIC4	-2.4457443	CACHD1	-1.3827784
RUNX3	-1.718995	LEPR	-0.5026305
RSRP1	-2.3808497	IL23R	-1.8219749
RHD	-0.8616529	PTGER3	-0.4769851
RHCE	-0.7393672	ZRANB2-AS2	-0.7692113
LDLRAP1	-0.524479	LRRIQ3	-4.5201473
MTFR1L	-0.9434078	CRYZ	-3.8312981
LOC646471	-0.7031969	ACADM	-1.2495409
SLC9A1	-0.830149	MSH4	-0.6743857
LOC105376892	-3.1722708	PIGK	-1.8635258
EYA3	-0.6216648	AK5	-2.5538728
PTAFR	-0.5985158	USP33	-0.6475346
TRNAU1AP	-1.0867337	LOC107985046	-0.8749856
GMEB1	-1.4408043	SPATA1	-1.0092144
EPB41	-1.51967	SSX2IP	-0.9152792
MECR	-1.4598365	WDR63	-0.8716801
PUM1	-4.6899919	ODF2L	-0.6659182
KIAA1522	-0.8985679	LOC105376828	-1.7576038
AZIN2	-2.2883567	CLCA3P	-0.6711587
TRIM62	-0.7328225	15-Sep	-1.7811821
ZNF362	-5.435399	LINC01140	-0.9429806
DLGAP3	-4.3273932	LOC105376833	-1.7394269
ZMYM4	-1.380125	PKN2-AS1	-1.2698792
KIAA0319L	-0.7947688	GTF2B	-0.7527746
AGO3	-2.3250951	GBP5	-1.2939746
MAP7D1	-0.9935452	LRRC8C	-1.7540376
SH3D21	-2.8112805	LOC107985744	-1.0714176
OSCP1	-1.5349443	ZNF644	-1.964319
INPP5B	-1.2898634	TGFBP3	-0.8275646
RHBDL2	-1.4277051	BCAR3	-0.9395784

FIG. 25 – 4 of 5

Gene	Fold change (Log2): Down-regulation
MEM56-RWD1	-4.0577547
PTBP2	-0.5035885
DPYD-AS1	-2.0592805
OC10537886	-0.9790734
SLC35A3	-0.4723138
TRMT13	-4.2260524
RTCA	-1.7576952
CDC14A	-2.9356095
SLC30A7	-1.5891811
RNPC3	-1.7803235
VAV3	-1.3416063
STXBP3	-1.925931
GNAI3	-1.9964455
OC10798516	-2.0248853
KCNC4	-2.4196001
LRIF1	-0.586836
RAP1A	-1.1743757
CTTNBP2NL	-0.3591523

FIG. 25 – 5 of 5

FIG. 26A



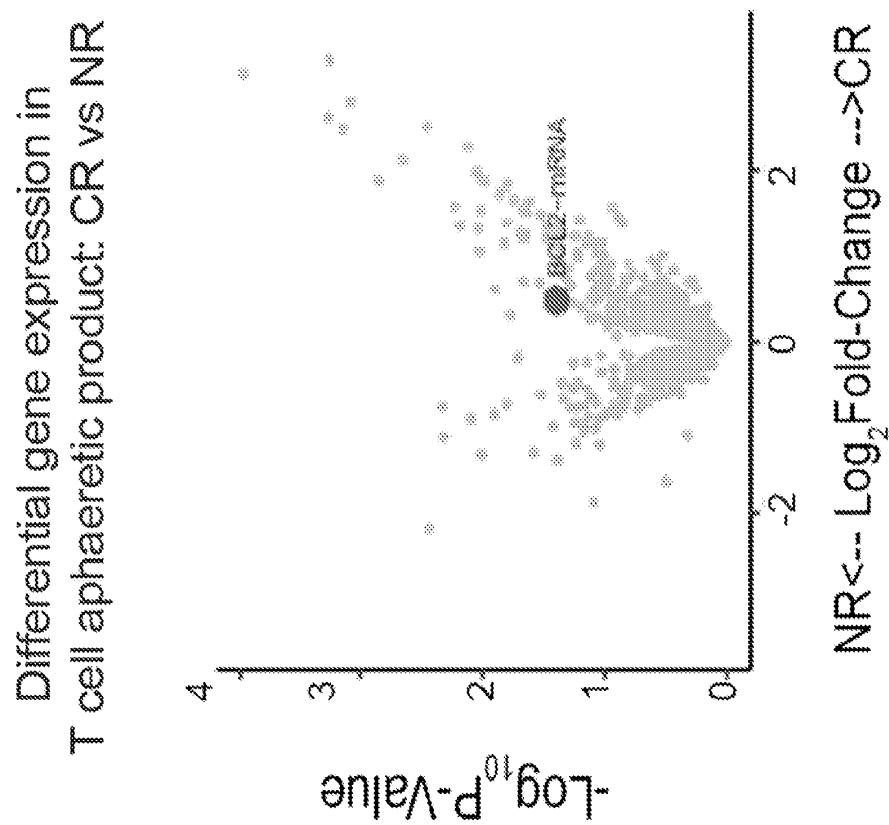
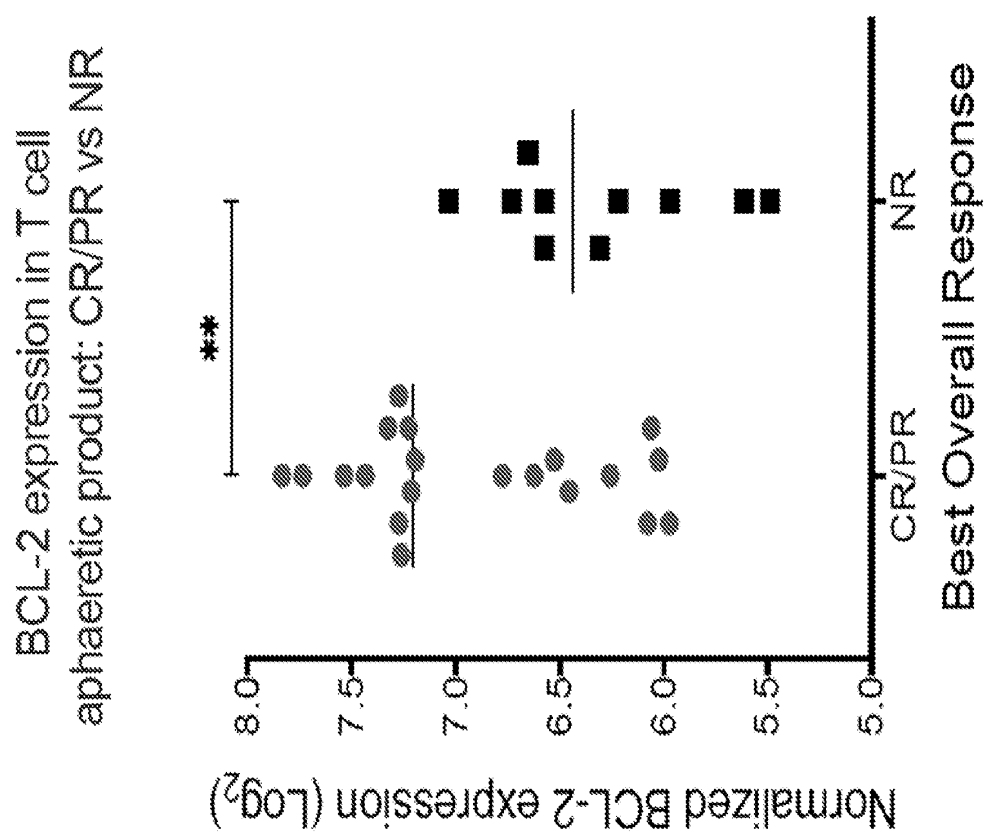


FIG. 26D

BCL-2 expression
correlates with CART persistence

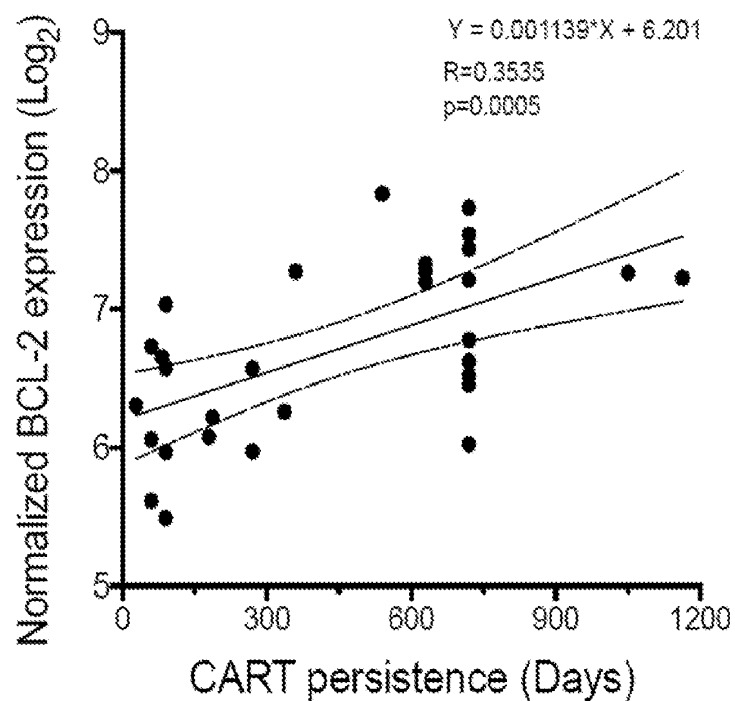


FIG. 26E

BCL-2 expression
correlates with overall survival

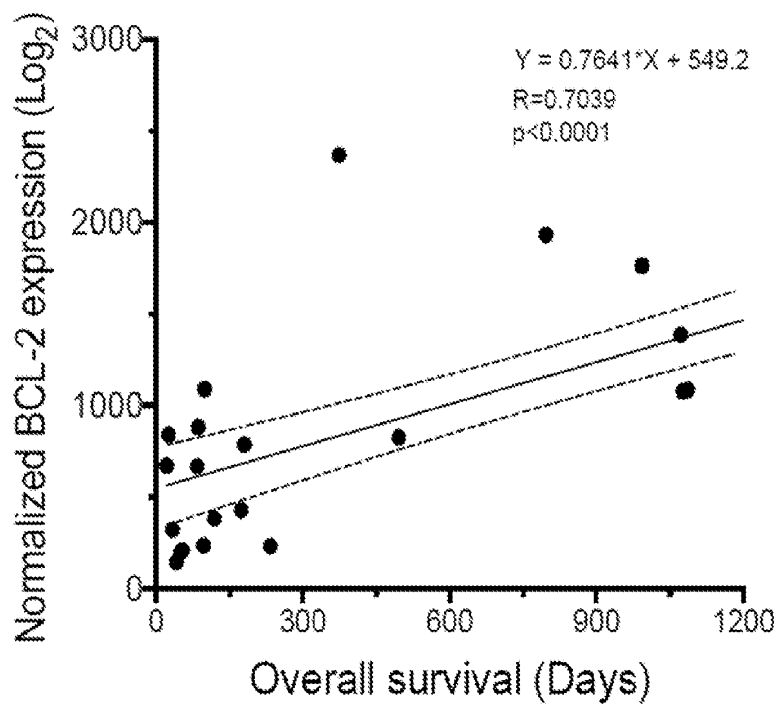
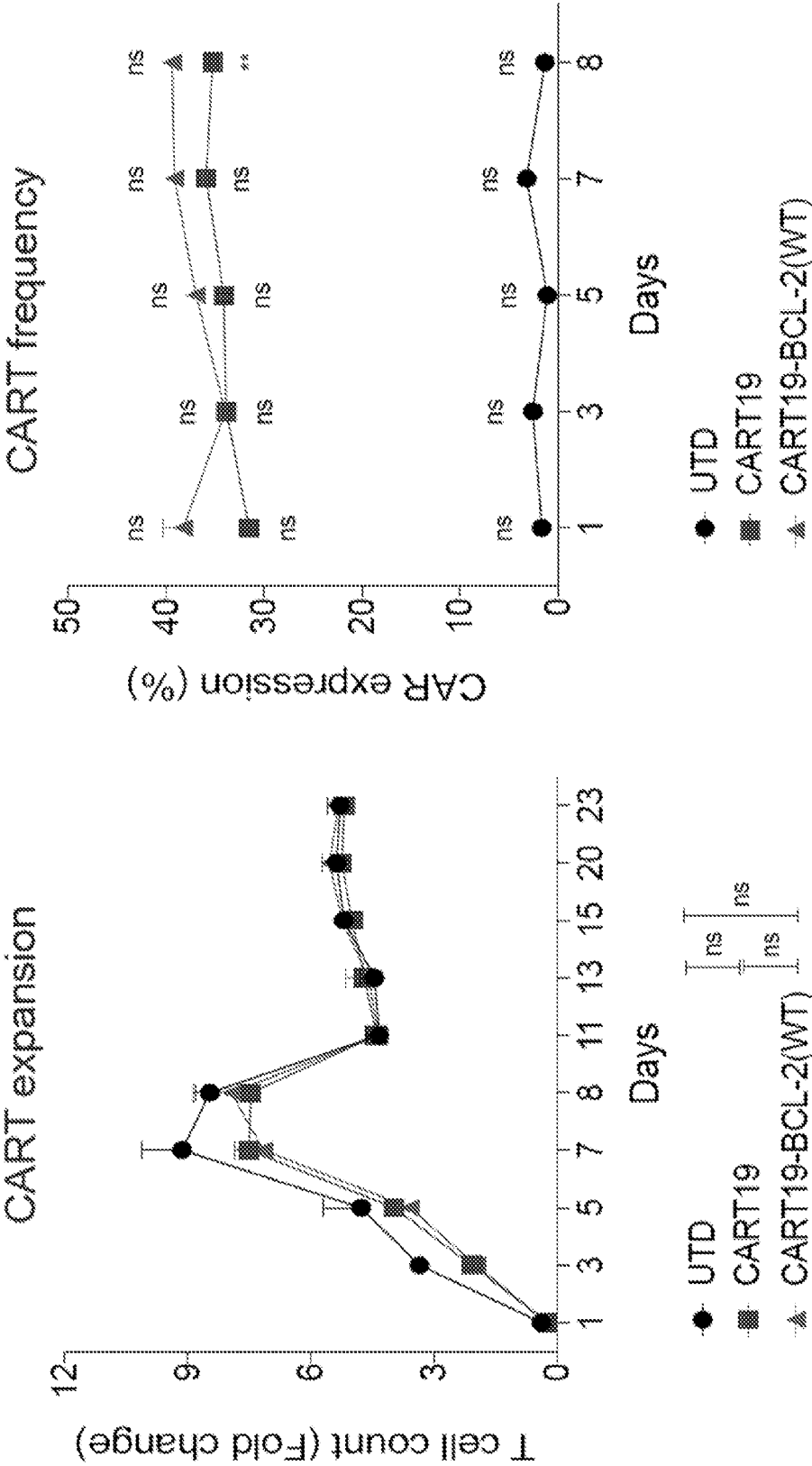


FIG. 26F

BCL-2(WT) overexpression does not induce abnormal CART expansion



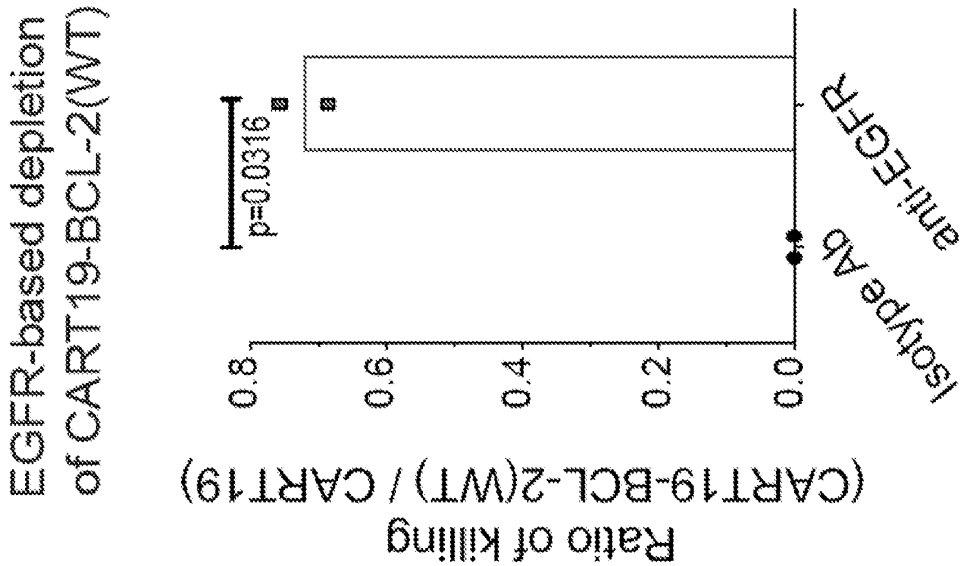


FIG. 26H

CART19-BCL-2(WT) are killed by chemotherapy

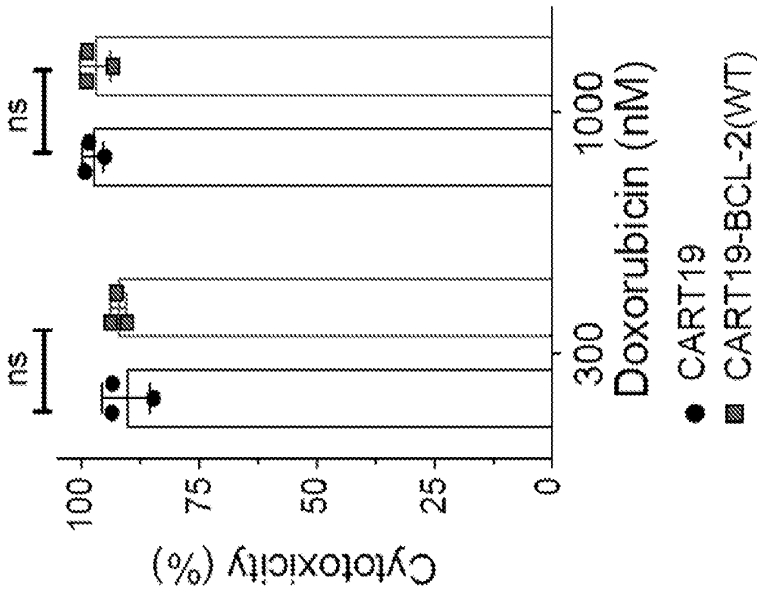


FIG. 26G

FIG. 27A

BCL-2 expression does not
correlates with CART peak expansion

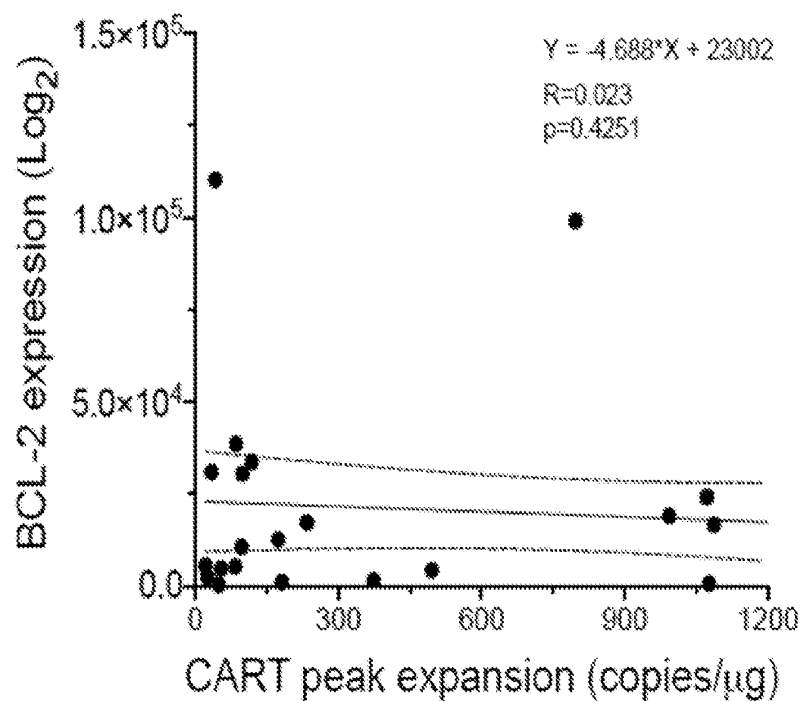
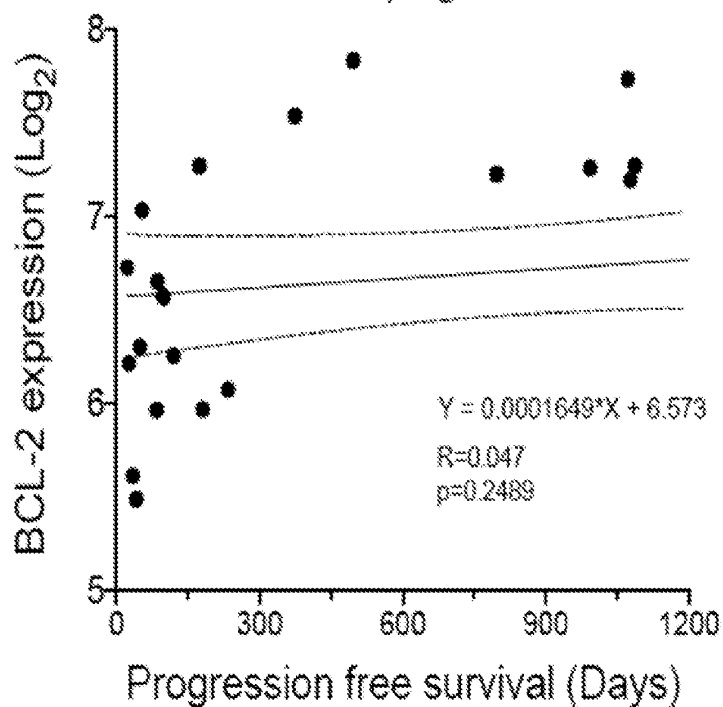


FIG. 27B

BCL-2 expression does not
correlates with progression free survival



No treatment of cytokines (IL7/IL15)

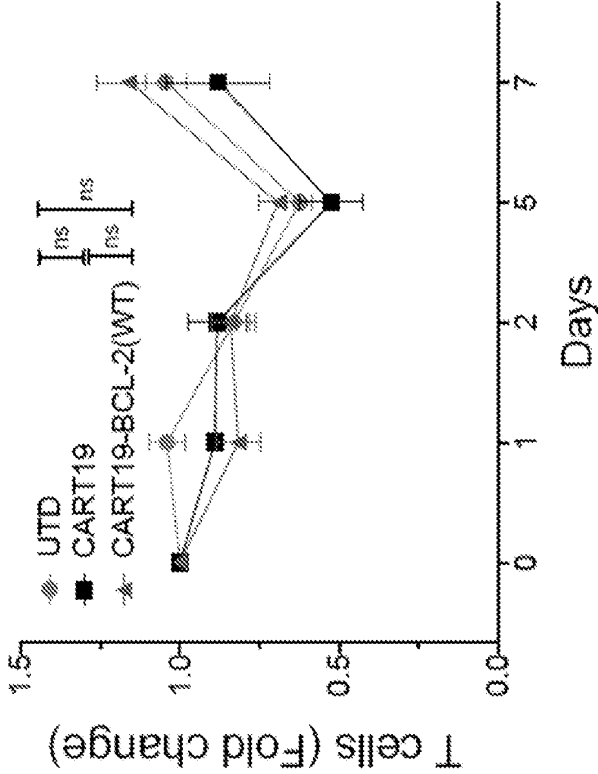


FIG. 28A

Treatment of cytokines (IL7/IL15)

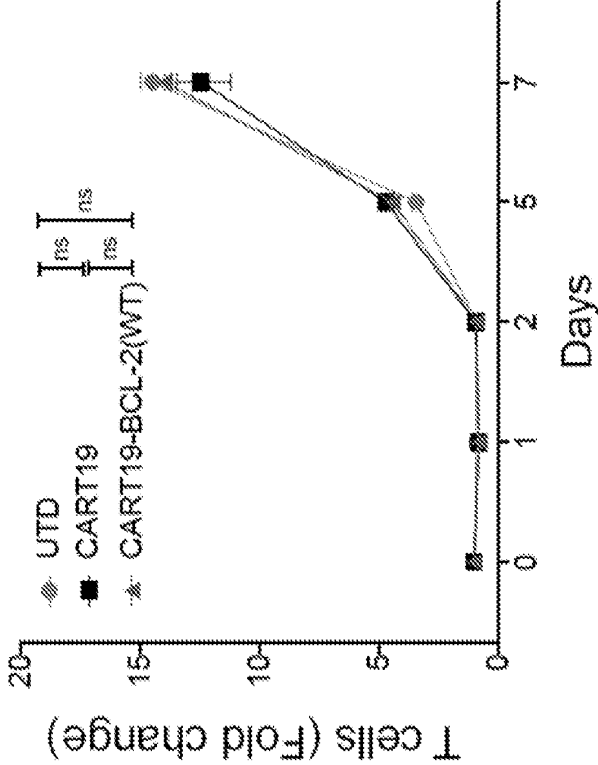


FIG. 28B