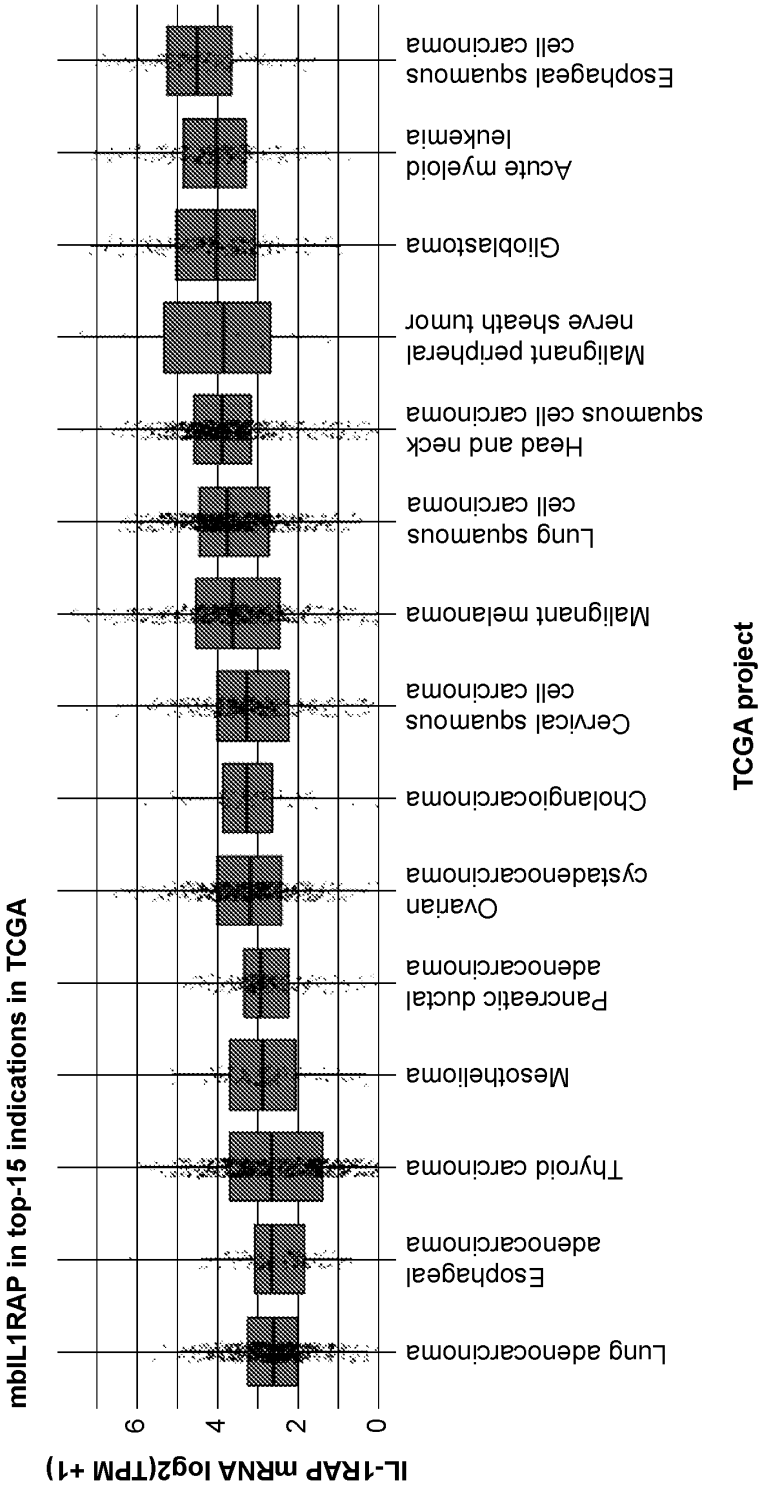

mbIL1RAP in top-15 indications in TCGA
IL-1RAP mRNA log2(TPM +1)
0
2
4
6
Lung adenocarcinoma
Esophageal adenocarcinoma
Thyroid carcinoma
Mesothelioma
Pancreatic ductal adenocarcinoma
Ovarian cystadenocarcinoma
Cholangiocarcinoma
Cervical squamous cell carcinoma
Malignant melanoma
Lung squamous cell carcinoma
Head and neck squamous cell carcinoma
Malignant peripheral nerve sheath tumor
Glioblastoma
Acute myeloid leukemia
Esophageal squamous cell carcinoma
TCGA project

FIG. 1A

IL-1RAP mRNA Log2(TPM+1)
0
2
4
6
8
Rhabdoid Cancer
Neuroblastoma
Mature B-Cell Neoplasms
Lung Neuroendocrine Tumor
B-Lymphoblastic Leukemia/Lymphoma
Hodgkin Lymphoma
Non-Hodgkin Lymphoma
Synovial Sarcoma
Colorectal Adenocarcinoma
Non-Seminomatous Germ Cell Tumor
T-Lymphoblastic Leukemia/Lymphoma
Rhabdomyosarcoma
Embryonal Tumor
Invasive Breast Carcinoma
Endometrial Carcinoma
Osteosarcoma
Renal Cell Carcinoma
Prostate Adenocarcinoma
Esophagogastric Adenocarcinoma
Ovarian Epithelial Tumor
Non-Small Cell Lung Cancer
Intracholecystic Papillary Neoplasm
Myeloproliferative Neoplasms
Pancreatic Adenocarcinoma
Intraductal Papillary Neoplasm of the Bi...
Well-Differentiated Thyroid Cancer
Hepatocellular Carcinoma
Pleural Mesothelioma
Acute Myeloid Leukemia
Cervical Squamous Cell Carcinoma
Liposarcoma
Nerve Sheath Tumor
Bladder Urothelial Carcinoma
Mature T and NK Neoplasms
Diffuse Glioma
Esophageal Squamous Cell Carcinoma
Anaplastic Thyroid Cancer
Ocular Melanoma
Head and Neck Squamous Cell Carcinoma
Melanoma
Ewing Sarcoma

FIG. 1B

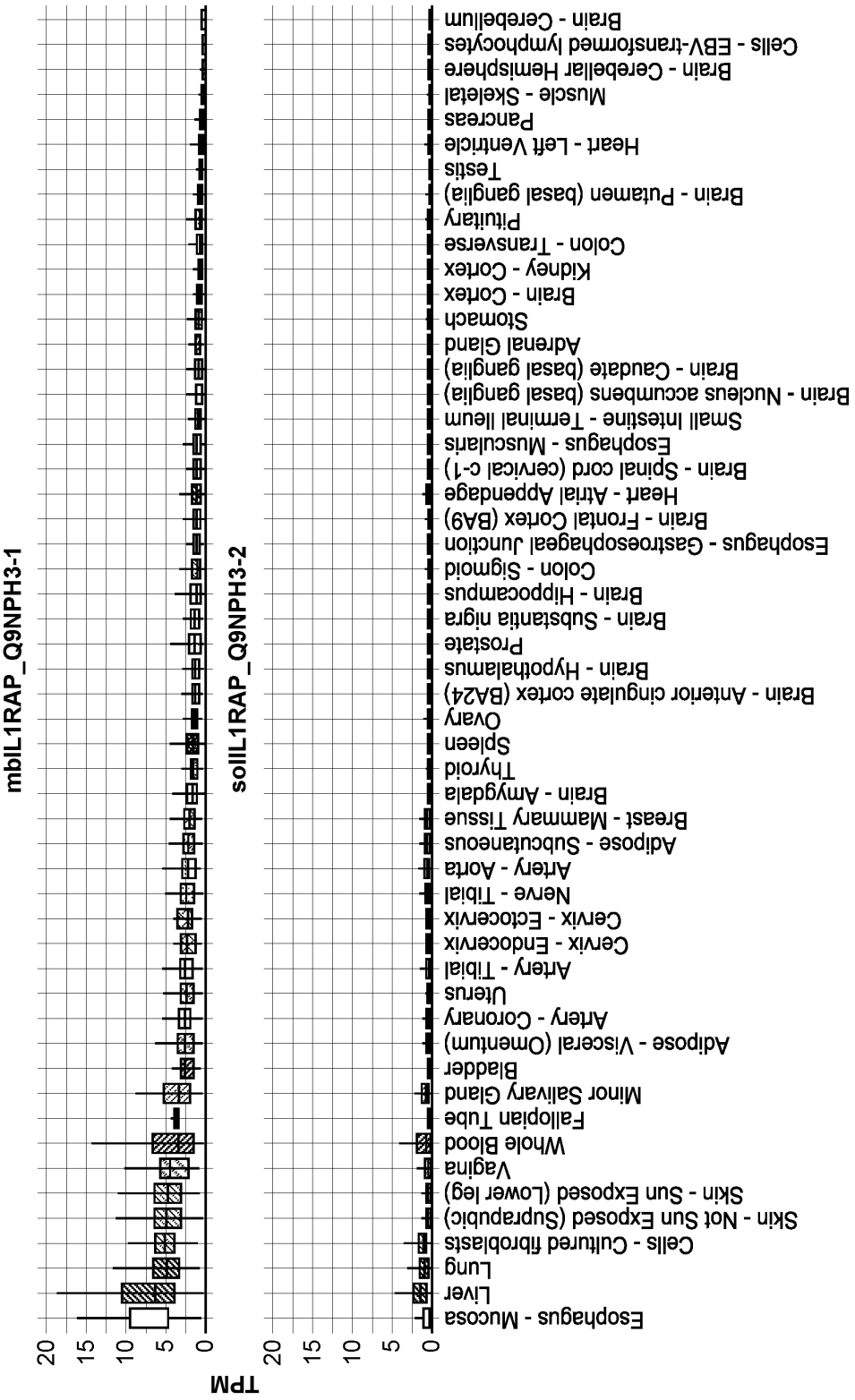

mbIL1RAP_Q9NPH3-1
solIL1RAP_Q9NPH3-2
TPM
0
5
10
15
20
Esophagus - Mucosa
Liver
Lung
Cells - Cultured fibroblasts
Skin - Not Sun Exposed (Suprapubic)
Skin - Sun Exposed (Lower leg)
Vagina
Whole Blood
Fallopian Tube
Minor Salivary Gland
Bladder
Adipose - Visceral (Omentum)
Artery - Coronary
Uterus
Artery - Tibial
Cervix - Endocervix
Cervix - Ectocervix
Nerve - Tibial
Artery - Aorta
Adipose - Subcutaneous
Breast - Mammary Tissue
Brain - Amygdala
Thyroid
Spleen
Ovary
Brain - Anterior cingulate cortex (BA24)
Brain - Hypothalamus
Prostate
Brain - Substantia nigra
Brain - Hippocampus
Colon - Sigmoid
Esophagus - Gastroesophageal Junction
Brain - Frontal Cortex (BA9)
Heart - Atrial Appendage
Brain - Spinal cord (cervical c-1)
Esophagus - Muscularis
Small Intestine - Terminal Ileum
Brain - Nucleus accumbens (basal ganglia)
Brain - Caudate (basal ganglia)
Adrenal Gland
Stomach
Brain - Cortex
Kidney - Cortex
Colon - Transverse
Pituitary
Brain - Putamen (basal ganglia)
Testis
Heart - Left Ventricle
Pancreas
Muscle - Skeletal
Brain - Cerebellar Hemisphere
Cells - EBV-transformed lymphocytes
Brain - Cerebellum
Tissue

FIG. 2

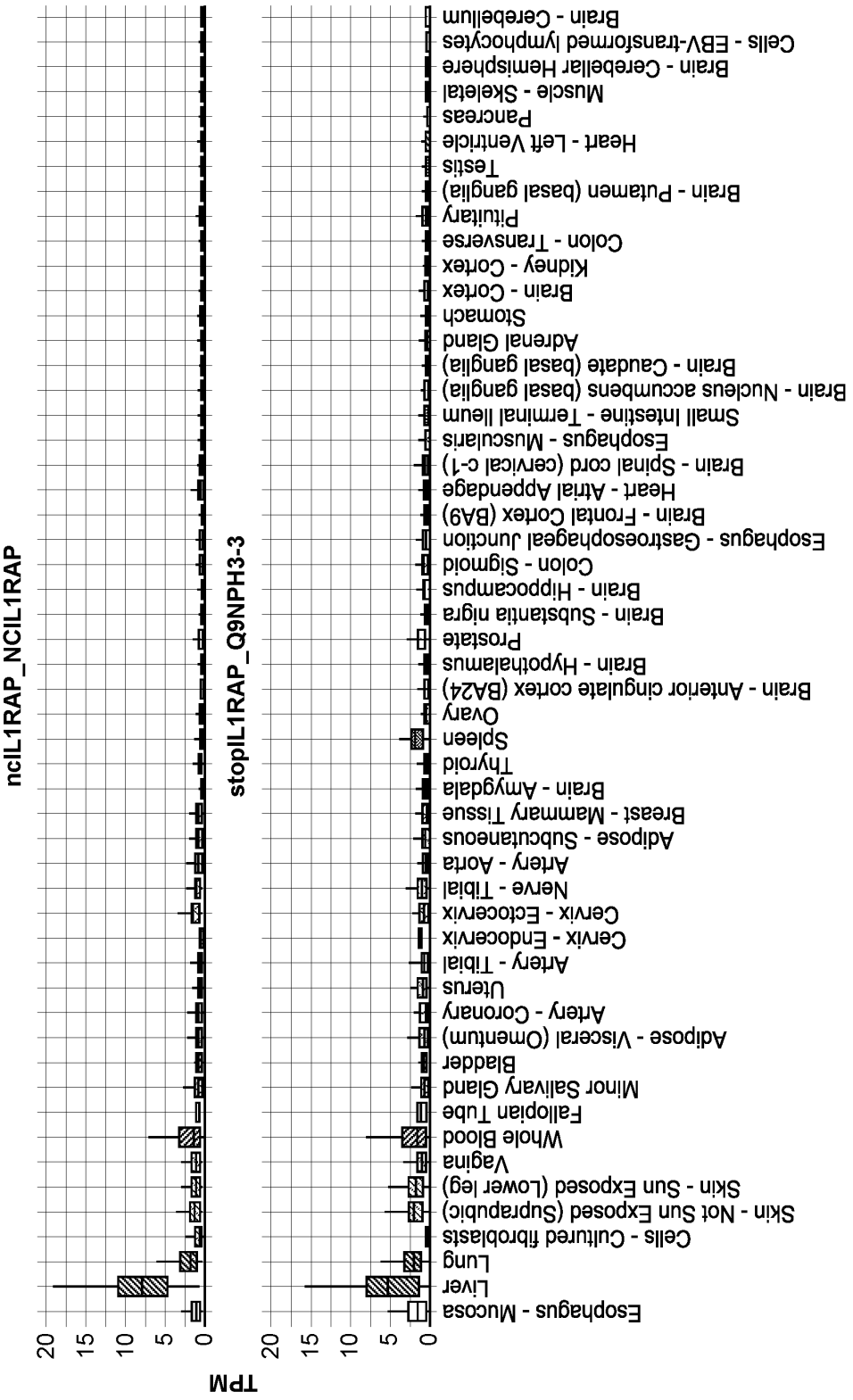

ncIL1RAP_NCIL1RAP
stopIL1RAP_Q9NPH3-3
TPM
0
5
10
15
20
Tissue
Esophagus - Mucosa
Liver
Lung
Cells - Cultured fibroblasts
Skin - Not Sun Exposed (Suprapubic)
Skin - Sun Exposed (Lower leg)
Vagina
Whole Blood
Fallopian Tube
Minor Salivary Gland
Bladder
Adipose - Visceral (Omentum)
Artery - Coronary
Uterus
Artery - Tibial
Cervix - Endocervix
Cervix - Ectocervix
Nerve - Tibial
Artery - Aorta
Adipose - Subcutaneous
Breast - Mammary Tissue
Brain - Amygdala
Thyroid
Spleen
Ovary
Brain - Anterior cingulate cortex (BA24)
Brain - Hypothalamus
Prostate
Brain - Substantia nigra
Brain - Hippocampus
Colon - Sigmoid
Esophagus - Gastroesophageal Junction
Brain - Frontal Cortex (BA9)
Heart - Atrial Appendage
Brain - Spinal cord (cervical c-1)
Esophagus - Muscularis
Small Intestine - Terminal Ileum
Brain - Nucleus accumbens (basal ganglia)
Brain - Caudate (basal ganglia)
Adrenal Gland
Stomach
Brain - Cortex
Kidney - Cortex
Colon - Transverse
Pituitary
Brain - Putamen (basal ganglia)
Testis
Heart - Left Ventricle
Pancreas
Muscle - Skeletal
Brain - Cerebellar Hemisphere
Cells - EBV-transformed lymphocytes
Brain - Cerebellum

FIG. 2 (Cont. 1)

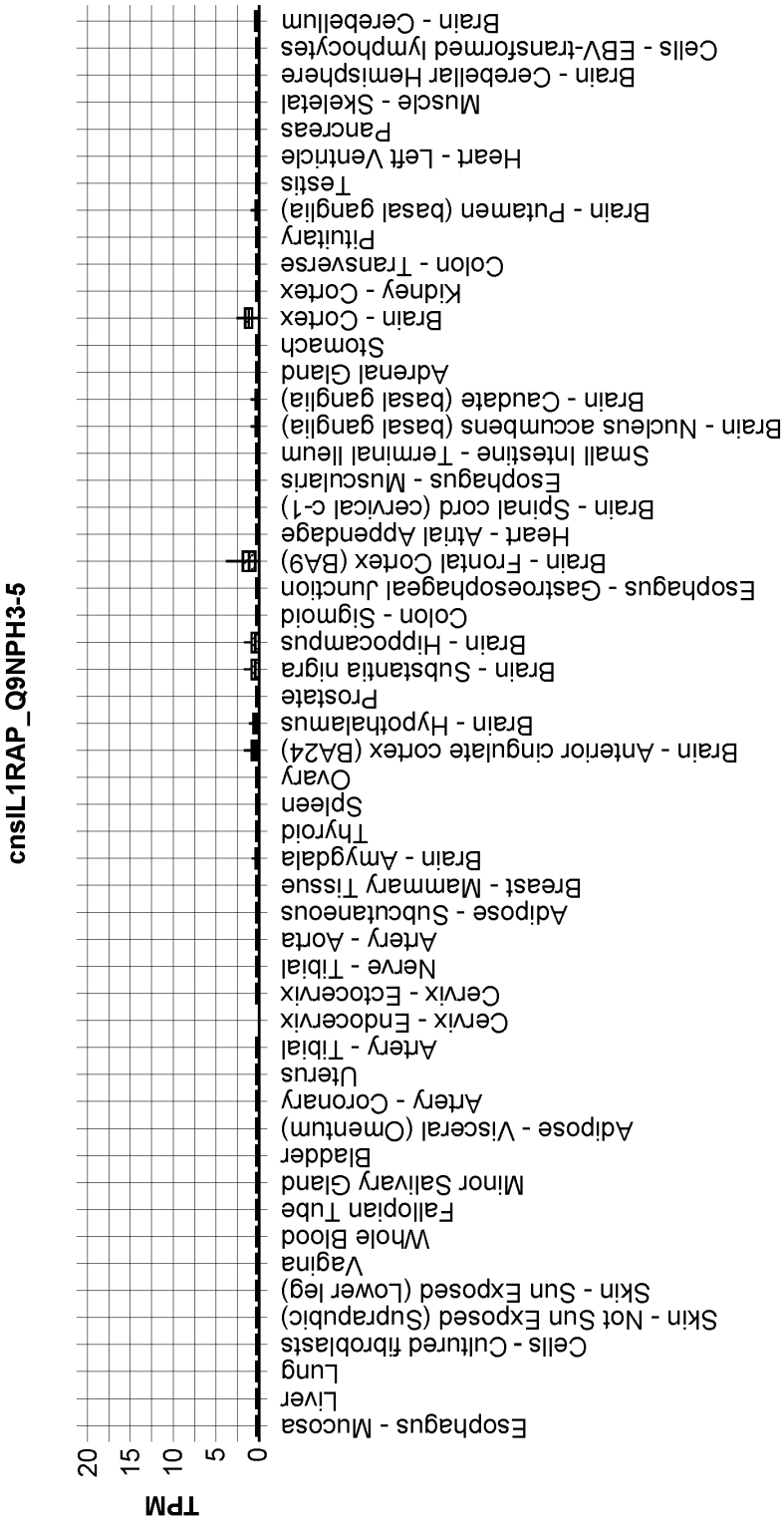

cnsIL1RAP_Q9NPH3-5
TPM
20
15
10
5
0
Esophagus - Mucosa
Liver
Lung
Cells - Cultured fibroblasts
Skin - Not Sun Exposed (Suprapubic)
Skin - Sun Exposed (Lower leg)
Vagina
Whole Blood
Fallopian Tube
Minor Salivary Gland
Bladder
Adipose - Visceral (Omentum)
Artery - Coronary
Uterus
Artery - Tibial
Cervix - Endocervix
Cervix - Ectocervix
Nerve - Tibial
Artery - Aorta
Adipose - Subcutaneous
Breast - Mammary Tissue
Brain - Amygdala
Thyroid
Spleen
Ovary
Brain - Anterior cingulate cortex (BA24)
Brain - Hypothalamus
Prostate
Brain - Substantia nigra
Brain - Hippocampus
Colon - Sigmoid
Esophagus - Gastroesophageal Junction
Brain - Frontal Cortex (BA9)
Heart - Atrial Appendage
Brain - Spinal cord (cervical c-1)
Esophagus - Muscularis
Small Intestine - Terminal Ileum
Brain - Nucleus accumbens (basal ganglia)
Brain - Caudate (basal ganglia)
Adrenal Gland
Stomach
Brain - Cortex
Kidney - Cortex
Colon - Transverse
Pituitary
Brain - Putamen (basal ganglia)
Testis
Heart - Left Ventricle
Pancreas
Muscle - Skeletal
Brain - Cerebellar Hemisphere
Cells - EBV-transformed lymphocytes
Brain - Cerebellum
Tissue

FIG. 2 (Cont. 2)

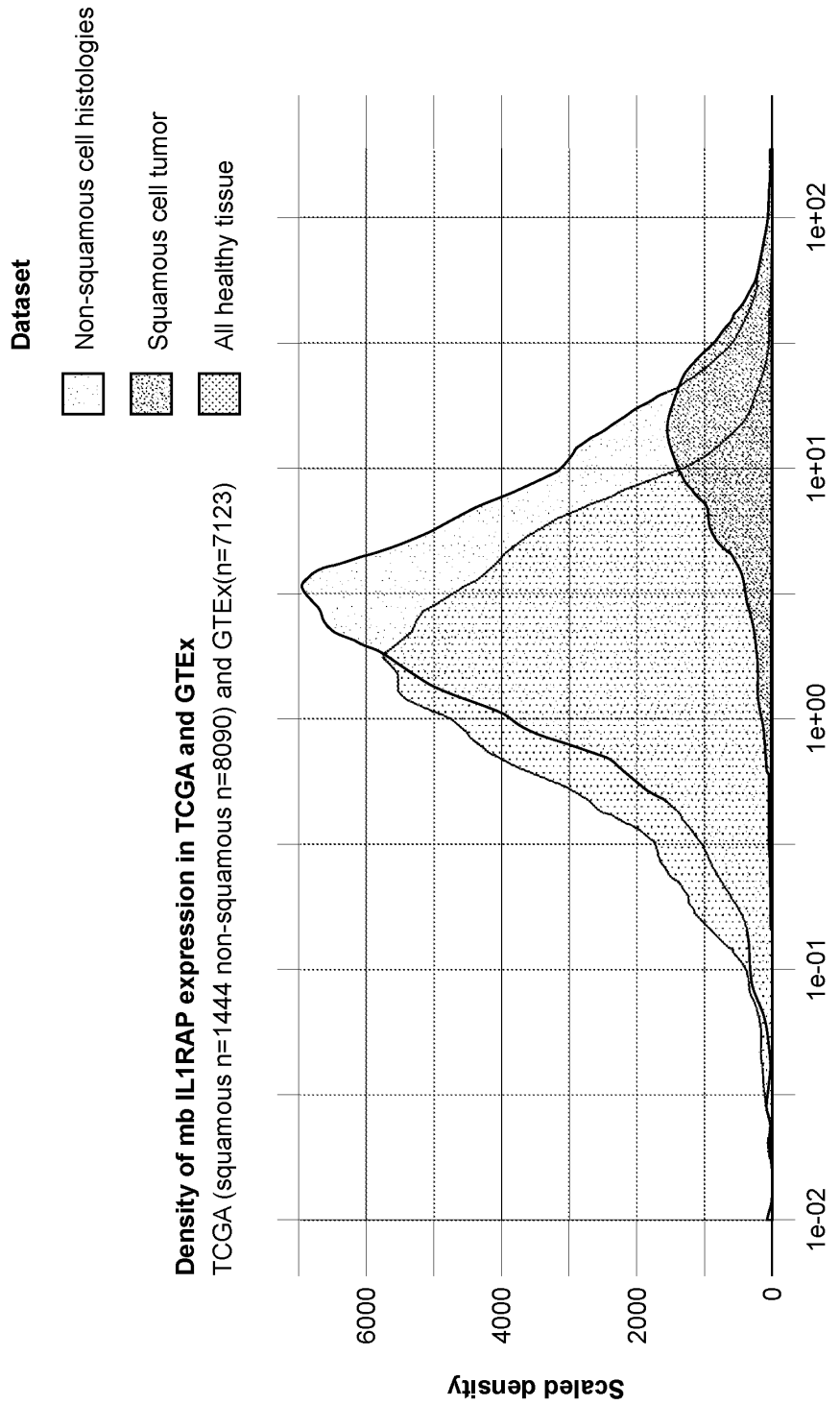

Dataset
Non-squamous cell histologies
Squamous cell tumor
All healthy tissue
Density of mb IL1RAP expression in TCGA and GTEx
TCGA (squamous n=1444 non-squamous n=8090) and GTEx(n=7123)
Scaled density
0
2000
4000
6000
1e-02
1e-01
1e+00
1e+01
1e+02
mbIL-1RAP TPM

FIG. 3

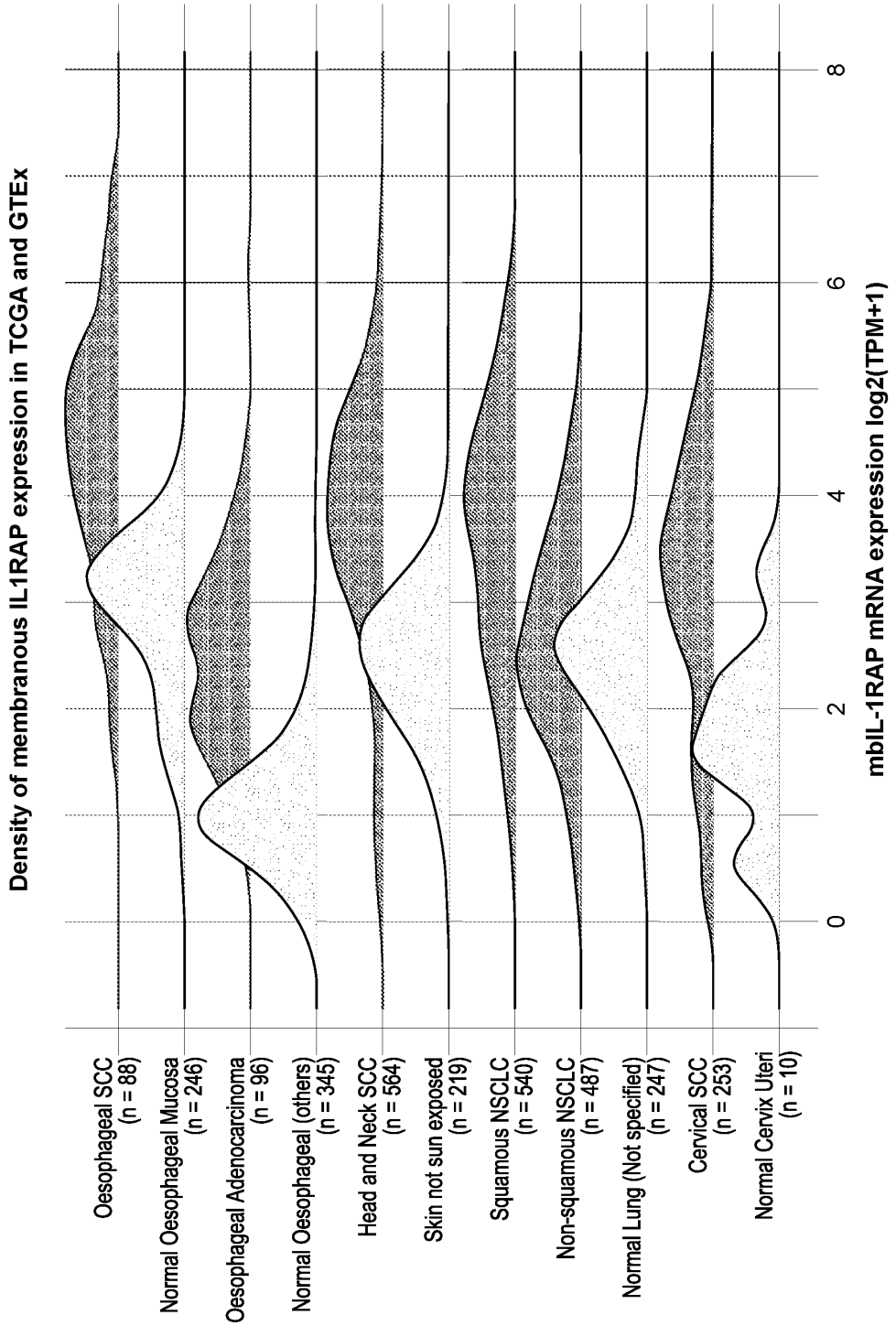

Density of membranous IL1RAP expression in TCGA and GTEx
Oesophageal SCC (n = 88)
Normal Oesophageal Mucosa (n = 246)
Oesophageal Adenocarcinoma (n = 96)
Normal Oesophageal (others) (n = 345)
Head and Neck SCC (n = 564)
Skin not sun exposed (n = 219)
Squamous NSCLC (n = 540)
Non-squamous NSCLC (n = 487)
Normal Lung (Not specified) (n = 247)
Cervical SCC (n = 253)
Normal Cervix Uteri (n = 10)
0
2
4
6
8
mbIL-1RAP mRNA expression log2(TPM+1)

FIG. 4

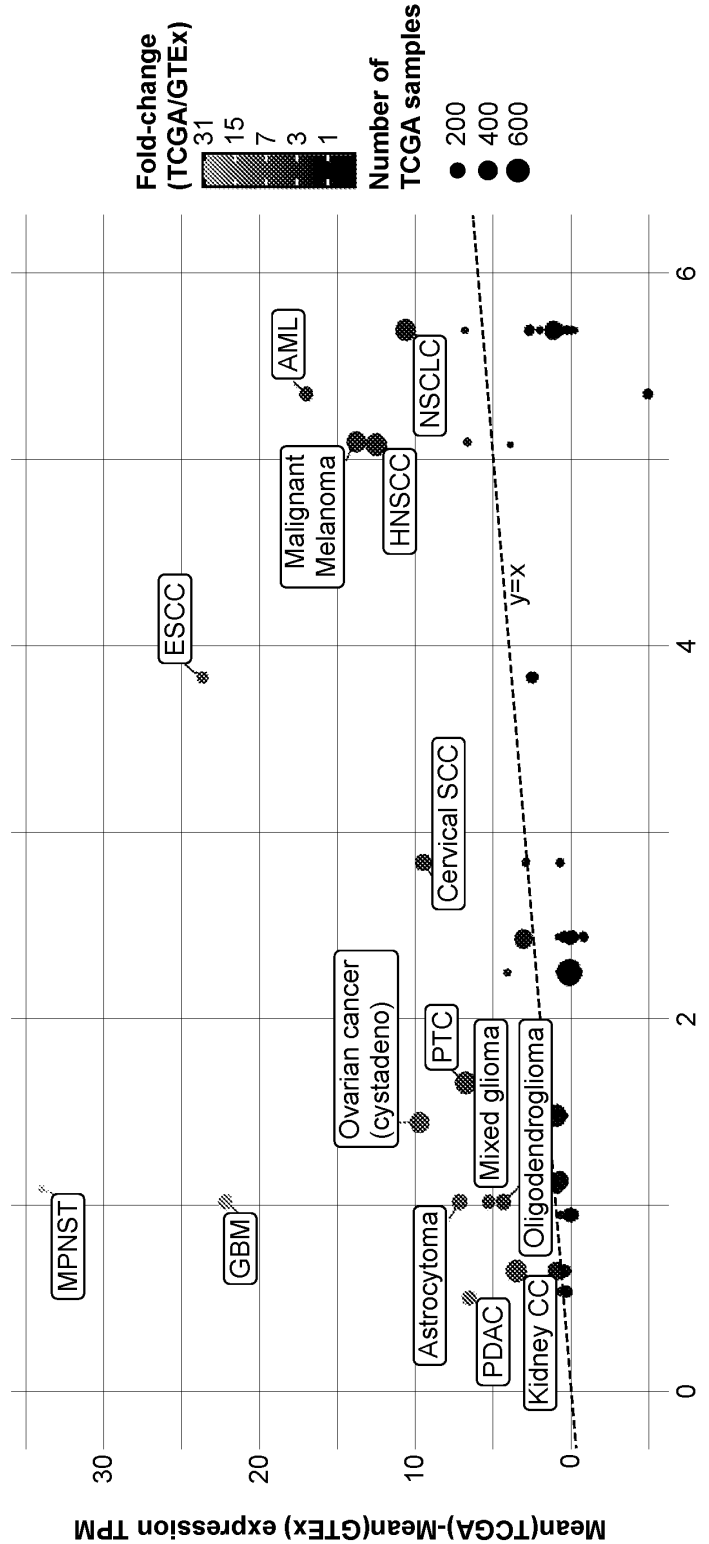

Fold-change (TCGA/GTEx)
31
15
7
3
1
Number of TCGA samples
200
400
600
MPNST
GBM
ESCC
Astrocytoma
PDAC
Ovarian cancer (cystadeno)
PTC
Mixed glioma
Kidney CC
Oligodendroglioma
Cervical SCC
Malignant Melanoma
AML
HNSCC
NSCLC
y=x
Mean(TCGA)-Mean(GTEx) expression TPM
Mean(GTEx) expression TPM
0
10
20
30
0
2
4
6

FIG. 5

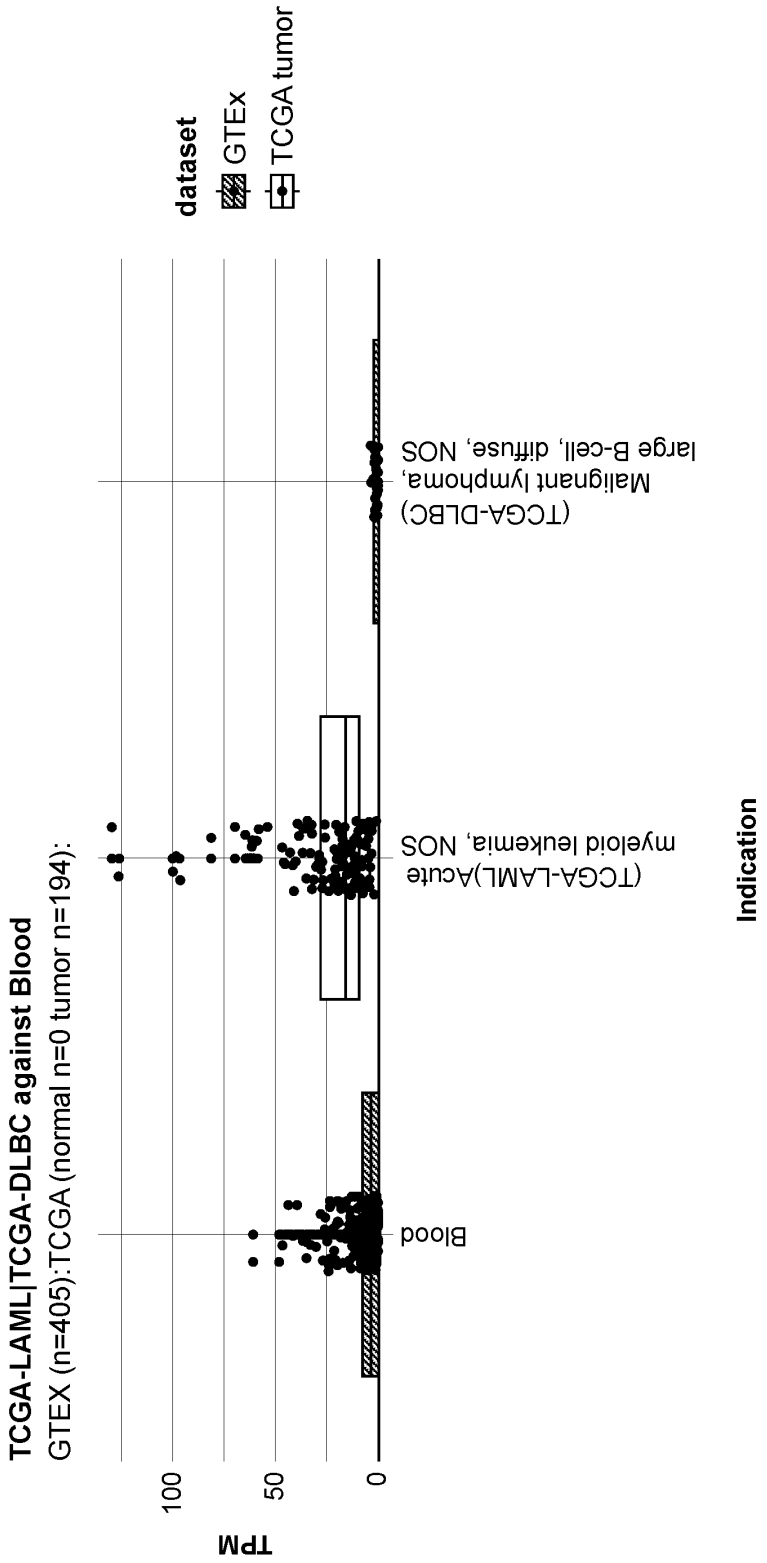

TCGA-LAML|TCGA-DLBC against Blood
GTEX (n=405):TCGA (normal n=0 tumor n=194):
TPM
100
50
0
Blood
(TCGA-LAML)Acute myeloid leukemia, NOS
(TCGA-DLBC) Malignant lymphoma, large B-cell, diffuse, NOS
Indication
dataset
GTEx
TCGA tumor

FIG. 6A

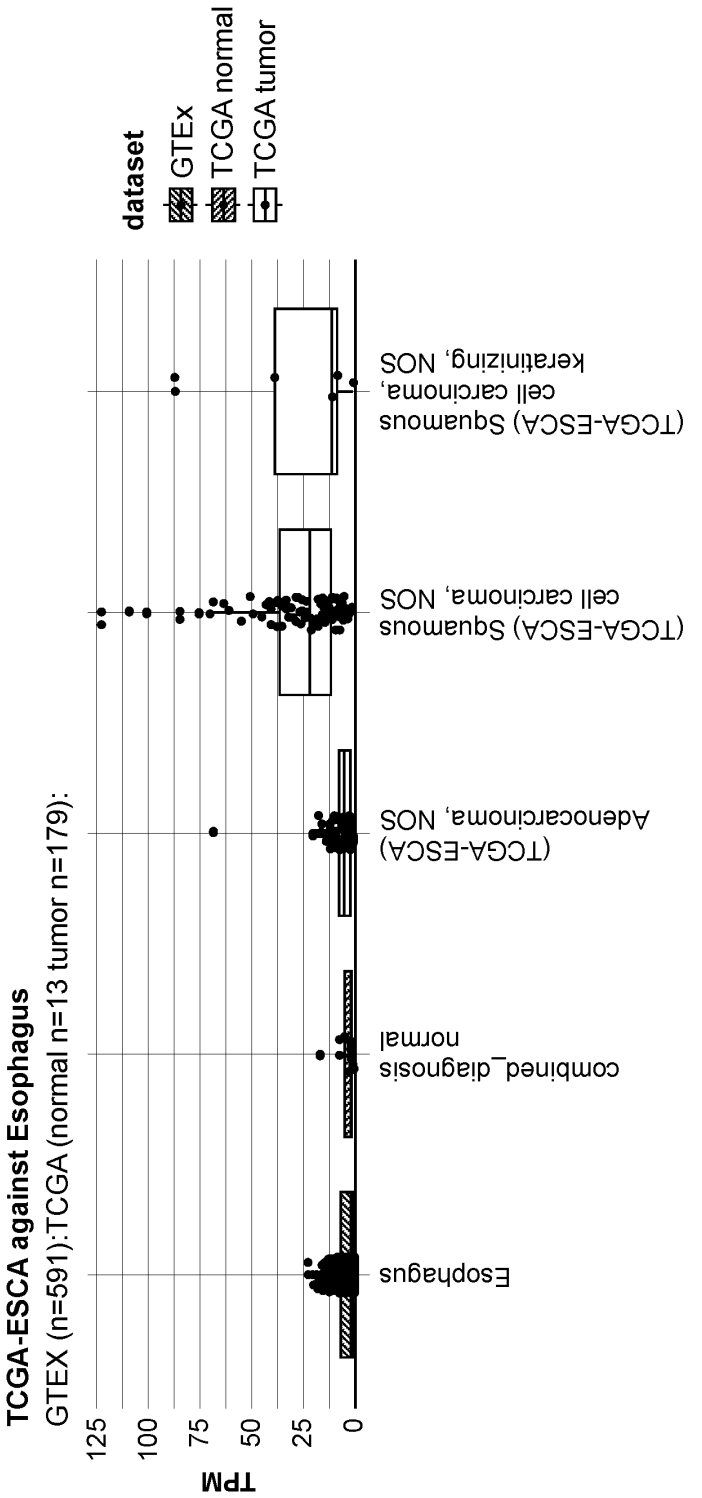

TCGA-ESCA against Esophagus
GTEX (n=591):TCGA (normal n=13 tumor n=179):
TPM
125
100
75
50
25
0
dataset
GTEx
TCGA normal
TCGA tumor
Esophagus
combined_diagnosis
normal
(TCGA-ESCA)
Adenocarcinoma, NOS
(TCGA-ESCA) Squamous
cell carcinoma, NOS
(TCGA-ESCA) Squamous
cell carcinoma,
keratinizing, NOS
Indication

FIG. 6B

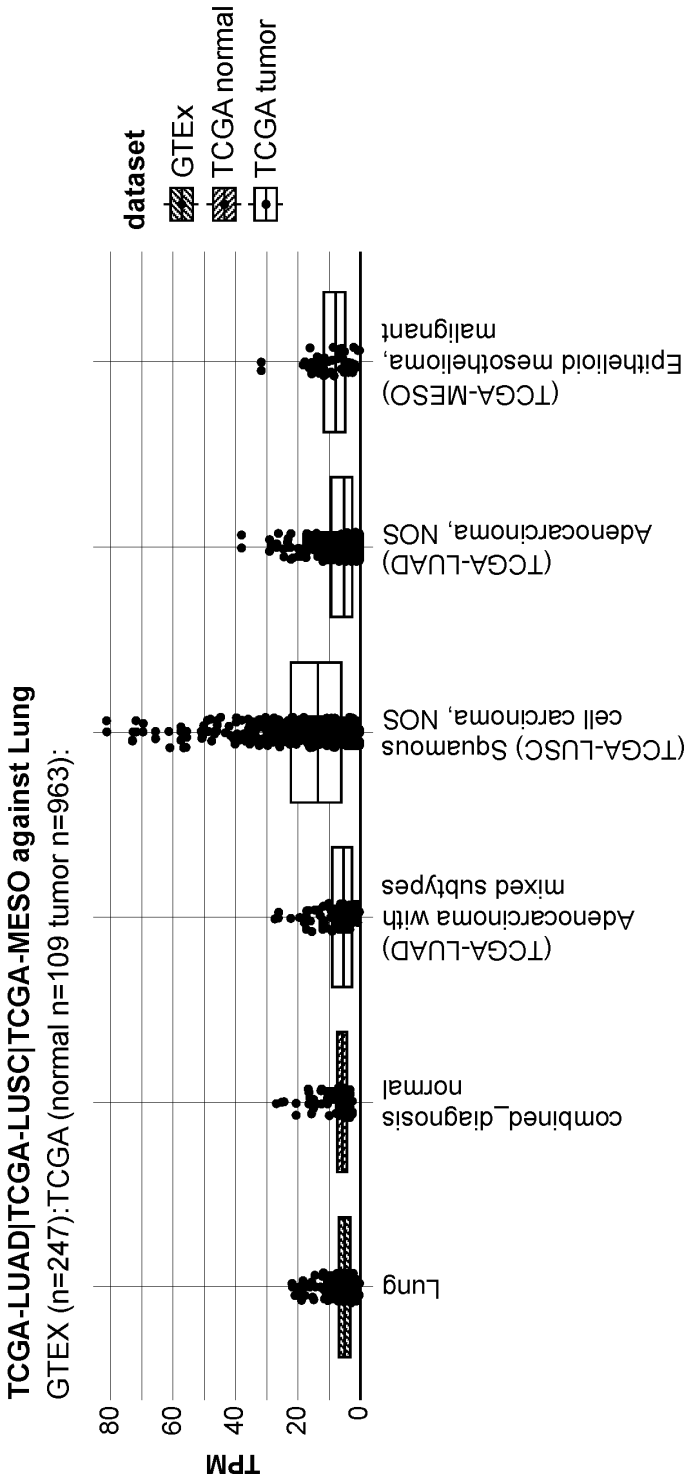

TCGA-LUAD|TCGA-LUSC|TCGA-MESO against Lung
GTEX (n=247):TCGA (normal n=109 tumor n=963):
TPM
0
20
40
60
80
dataset
GTEx
TCGA normal
TCGA tumor
Lung
combined_diagnosis
normal
(TCGA-LUAD)
Adenocarcinoma with
mixed subtypes
(TCGA-LUSC) Squamous
cell carcinoma, NOS
(TCGA-LUAD)
Adenocarcinoma, NOS
(TCGA-MESO)
Epithelioid mesothelioma,
malignant
Indication

FIG. 6C

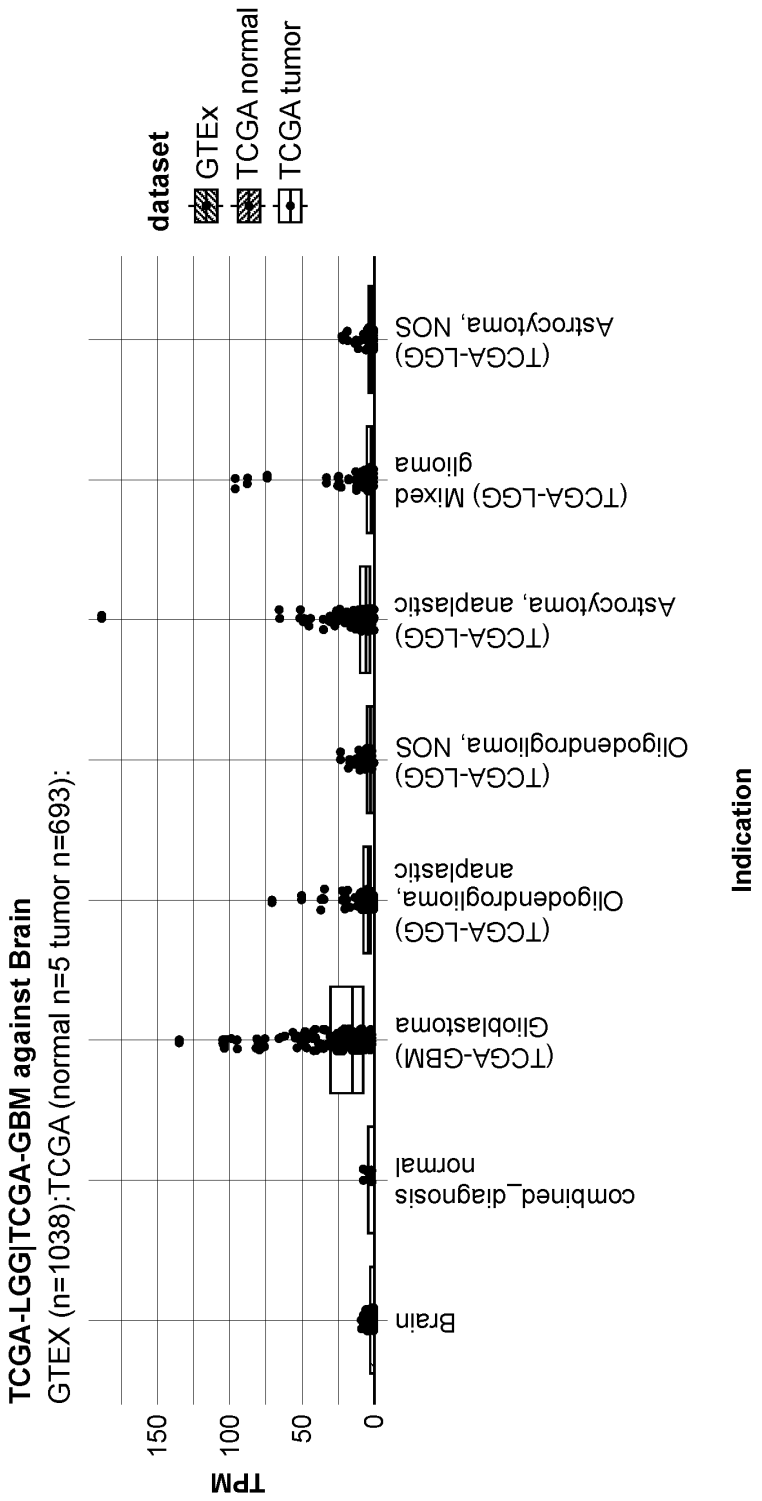

TCGA-LGG|TCGA-GBM against Brain
GTEX (n=1038):TCGA (normal n=5 tumor n=693):
dataset
GTEx
TCGA normal
TCGA tumor
TPM
150
100
50
0
Brain
combined_diagnosis
normal
(TCGA-GBM)
Glioblastoma
(TCGA-LGG)
Oligodendroglioma,
anaplastic
(TCGA-LGG)
Oligodendroglioma, NOS
(TCGA-LGG)
Astrocytoma, anaplastic
(TCGA-LGG) Mixed
glioma
(TCGA-LGG)
Astrocytoma, NOS
Indication

FIG. 6D

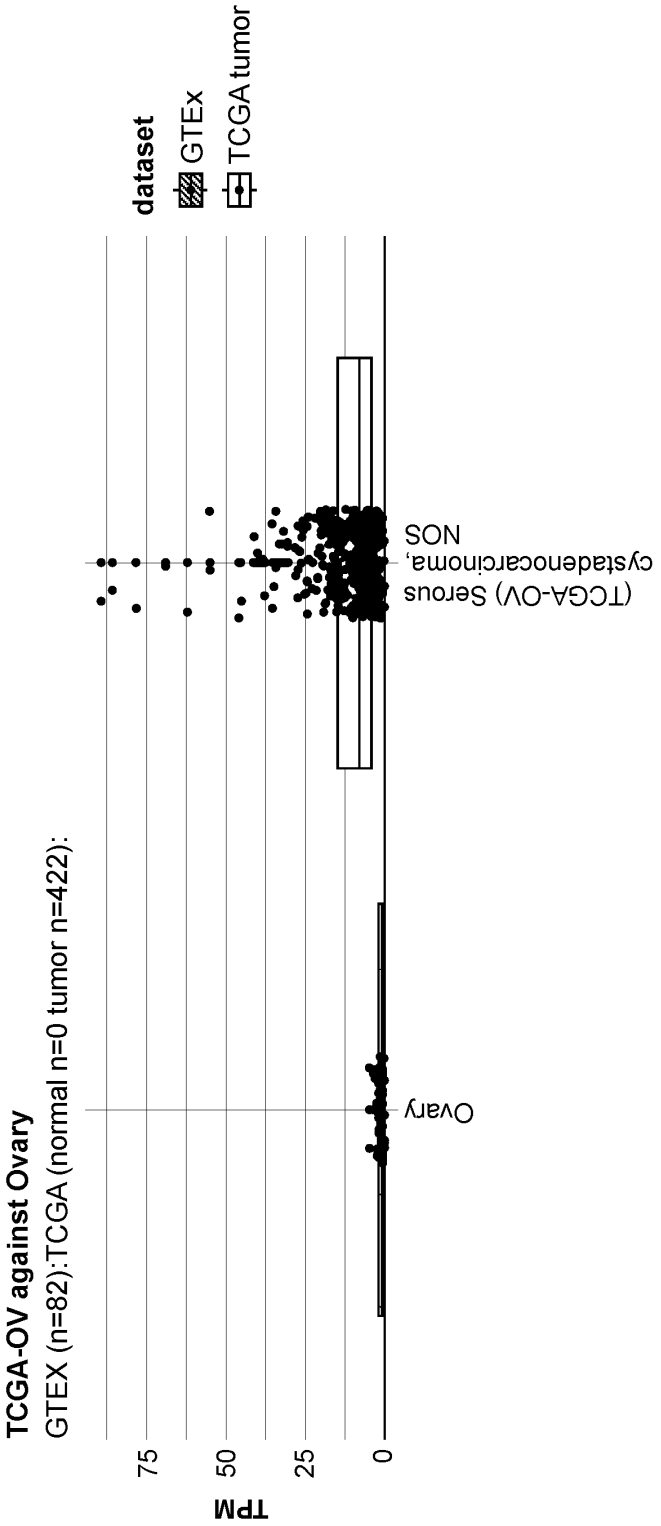

TCGA-OV against Ovary
GTEX (n=82):TCGA (normal n=0 tumor n=422):
dataset
GTEx
TCGA tumor
TPM
75
50
25
0
Ovary
(TCGA-OV) Serous cystadenocarcinoma, NOS
Indication

FIG. 6E

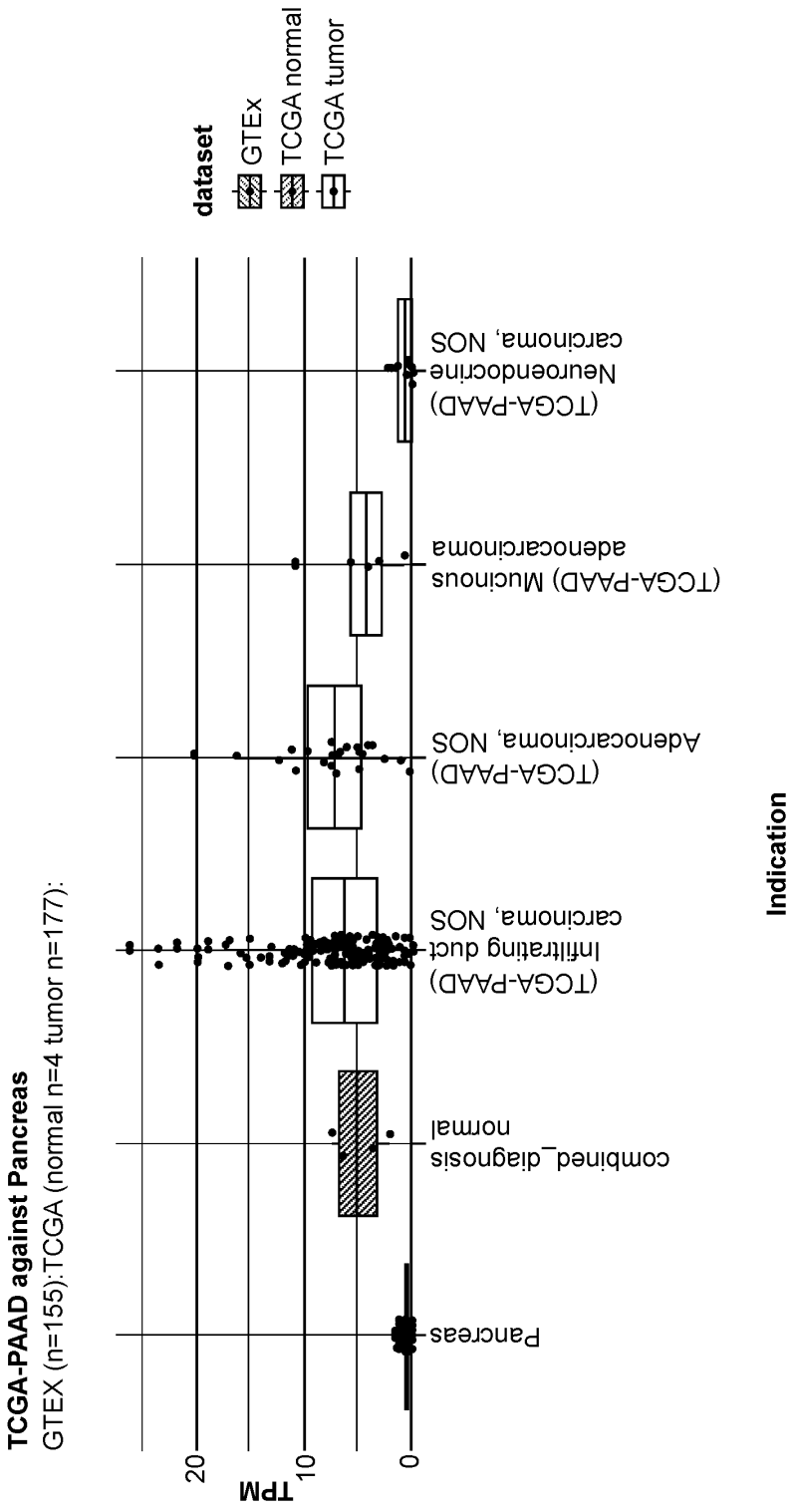

TCGA-PAAD against Pancreas
GTEX (n=155):TCGA (normal n=4 tumor n=177):
dataset
GTEx
TCGA normal
TCGA tumor
TPM
0
10
20
Pancreas
combined_diagnosis
normal
(TCGA-PAAD)
Infiltrating duct
carcinoma, NOS
(TCGA-PAAD)
Adenocarcinoma, NOS
(TCGA-PAAD) Mucinous
adenocarcinoma
(TCGA-PAAD)
Neuroendocrine
carcinoma, NOS
Indication

FIG. 6F

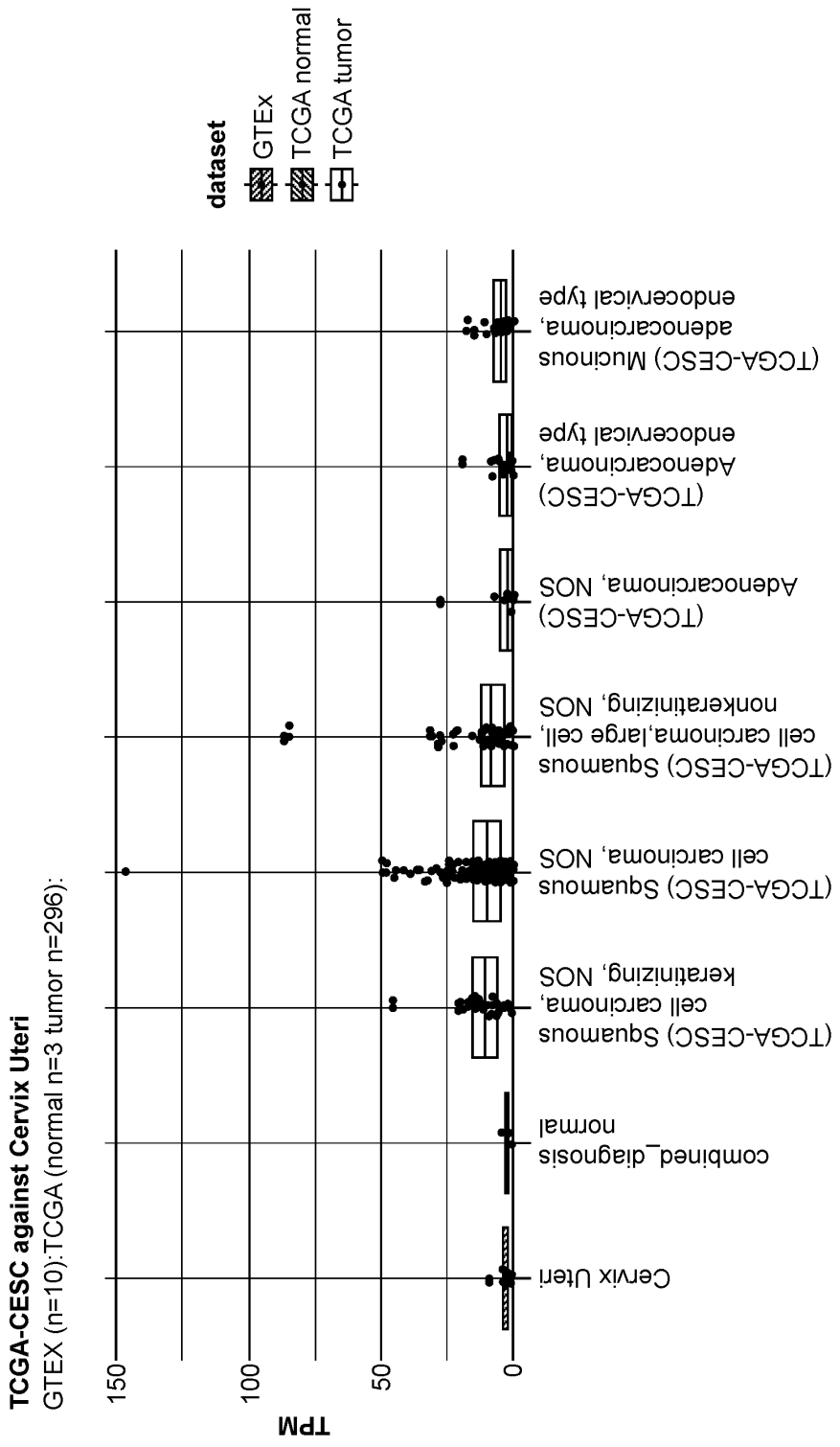

TCGA-CESC against Cervix Uteri
GTEX (n=10):TCGA (normal n=3 tumor n=296):
TPM
150
100
50
0
dataset
GTEx
TCGA normal
TCGA tumor
Cervix Uteri
combined_diagnosis
normal
(TCGA-CESC) Squamous cell carcinoma, keratinizing, NOS
(TCGA-CESC) Squamous cell carcinoma, NOS
(TCGA-CESC) Squamous cell carcinoma,large cell, nonkeratinizing, NOS
(TCGA-CESC) Adenocarcinoma, NOS
(TCGA-CESC) Adenocarcinoma, endocervical type
(TCGA-CESC) Mucinous adenocarcinoma, endocervical type
Indication

FIG. 6G

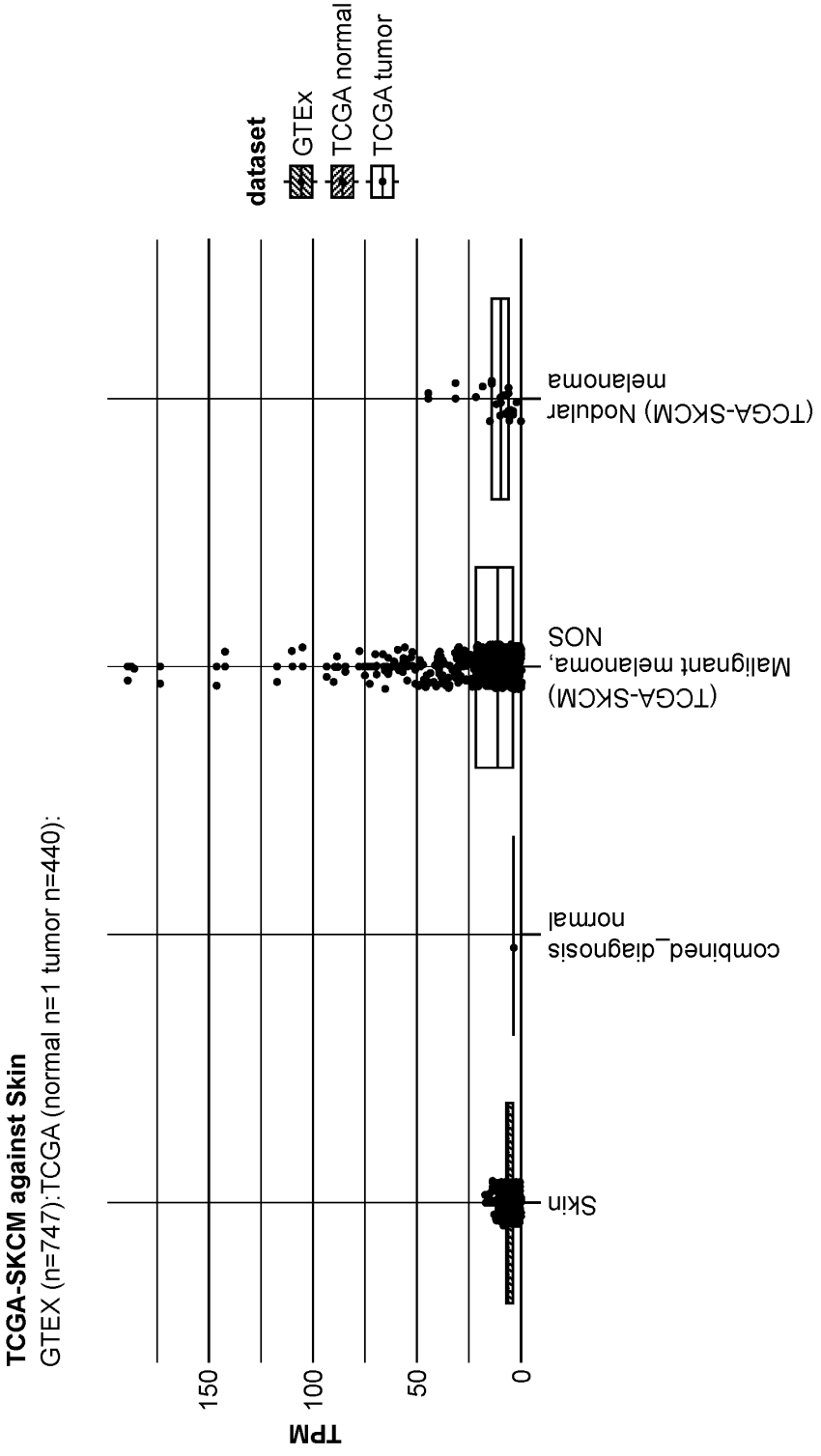

TCGA-SKCM against Skin
GTEX (n=747):TCGA (normal n=1 tumor n=440):
dataset
GTEx
TCGA normal
TCGA tumor
TPM
150
100
50
0
Skin
combined_diagnosis
normal
(TCGA-SKCM)
Malignant melanoma,
NOS
(TCGA-SKCM) Nodular
melanoma
Indication

FIG. 6H

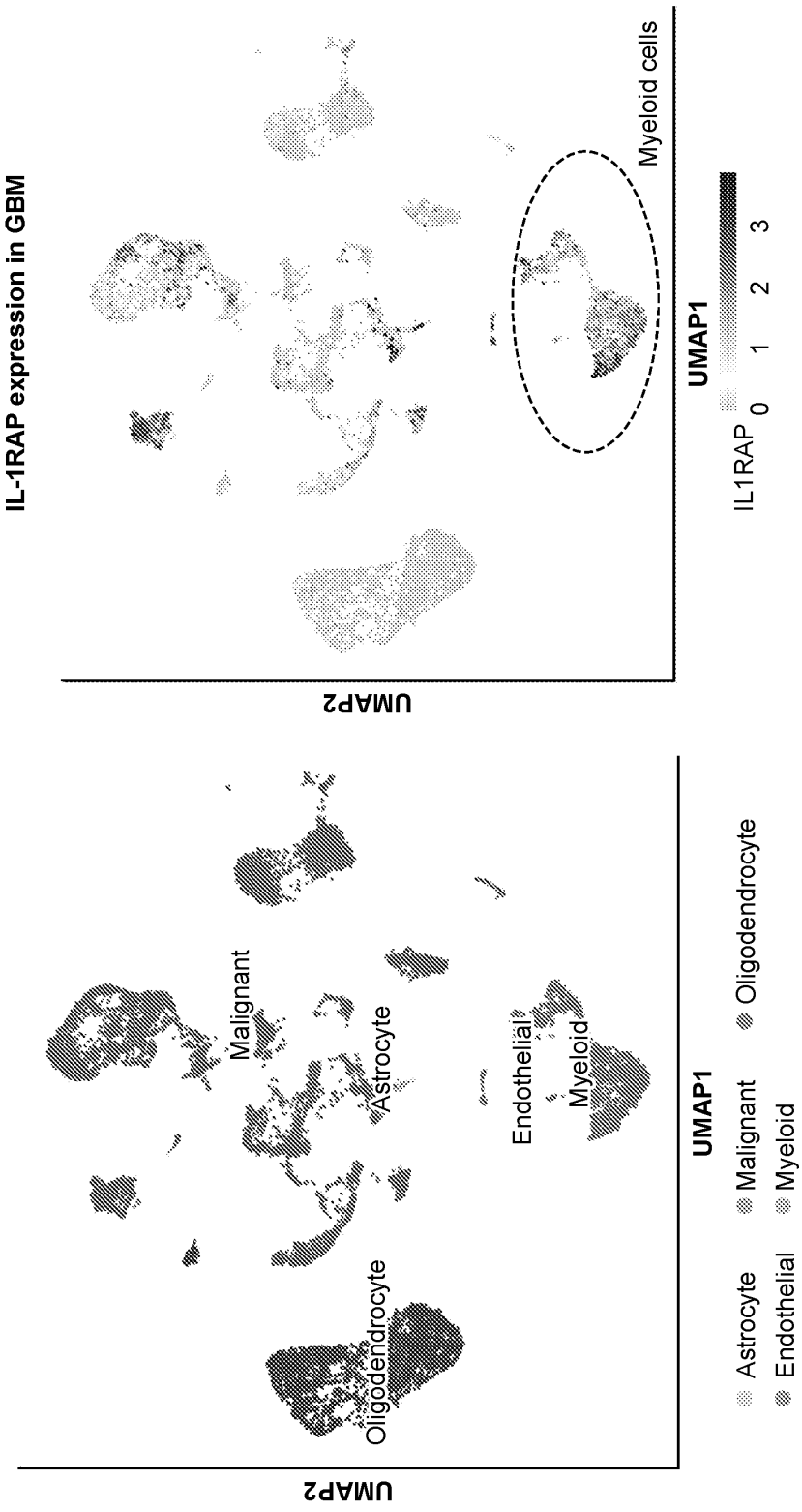

IL-1RAP expression in GBM
Myeloid cells
UMAP2
UMAP1
IL1RAP
0
1
2
3
Malignant
Astrocyte
Endothelial
Myeloid
Oligodendrocyte
UMAP2
UMAP1
Astrocyte
Malignant
Oligodendrocyte
Endothelial
Myeloid

FIG. 7A

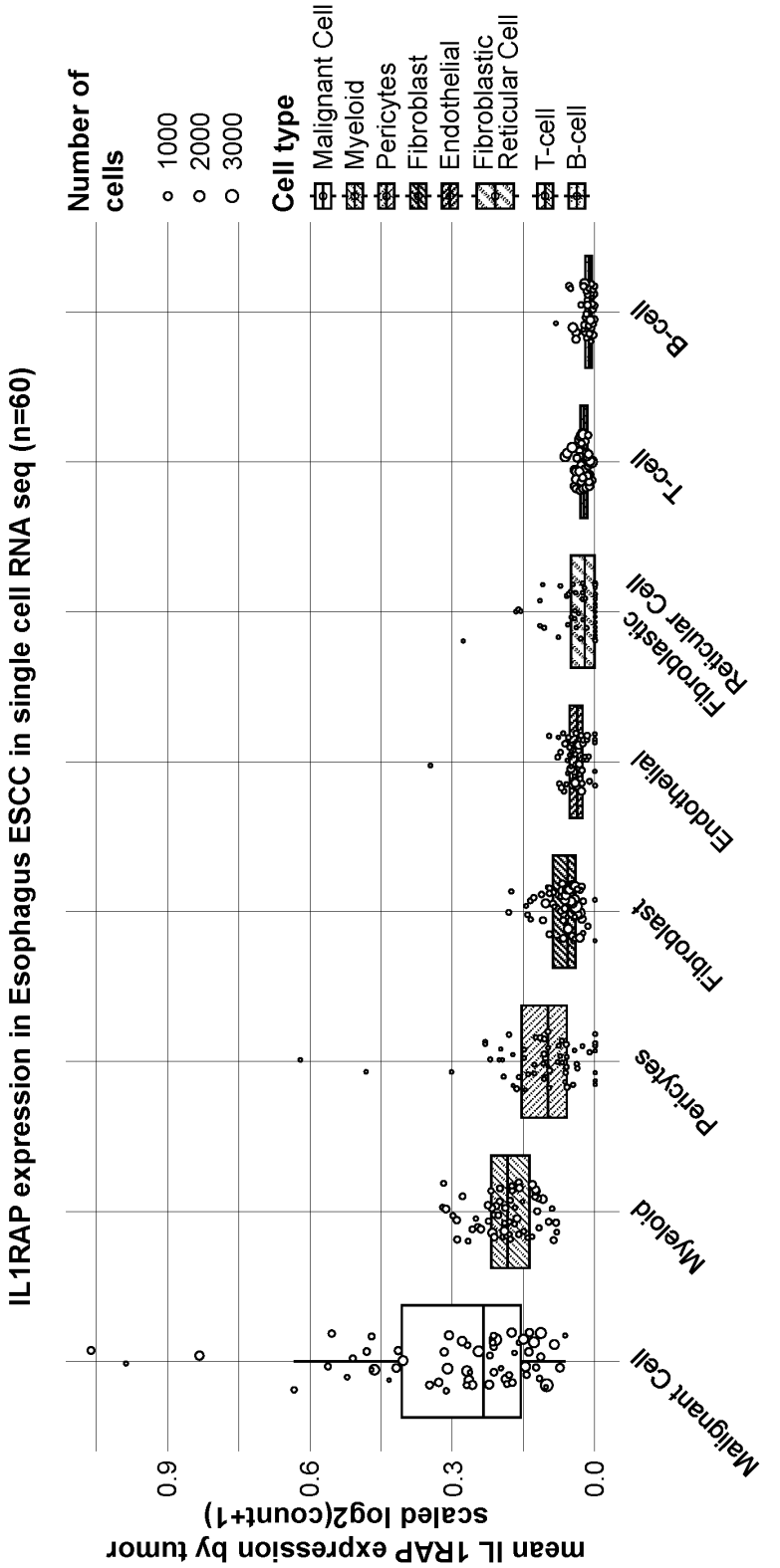

IL1RAP expression in Esophagus ESCC in single cell RNA seq (n=60)
mean IL 1RAP expression by tumor
scaled log2(count+1)
0.0
0.3
0.6
0.9
Malignant Cell
Myeloid
Pericytes
Fibroblast
Endothelial
Fibroblastic Reticular Cell
T-cell
B-cell
Cell type
Number of cells
1000
2000
3000
Cell type
Malignant Cell
Myeloid
Pericytes
Fibroblast
Endothelial
Fibroblastic Reticular Cell
T-cell
B-cell

FIG. 7B

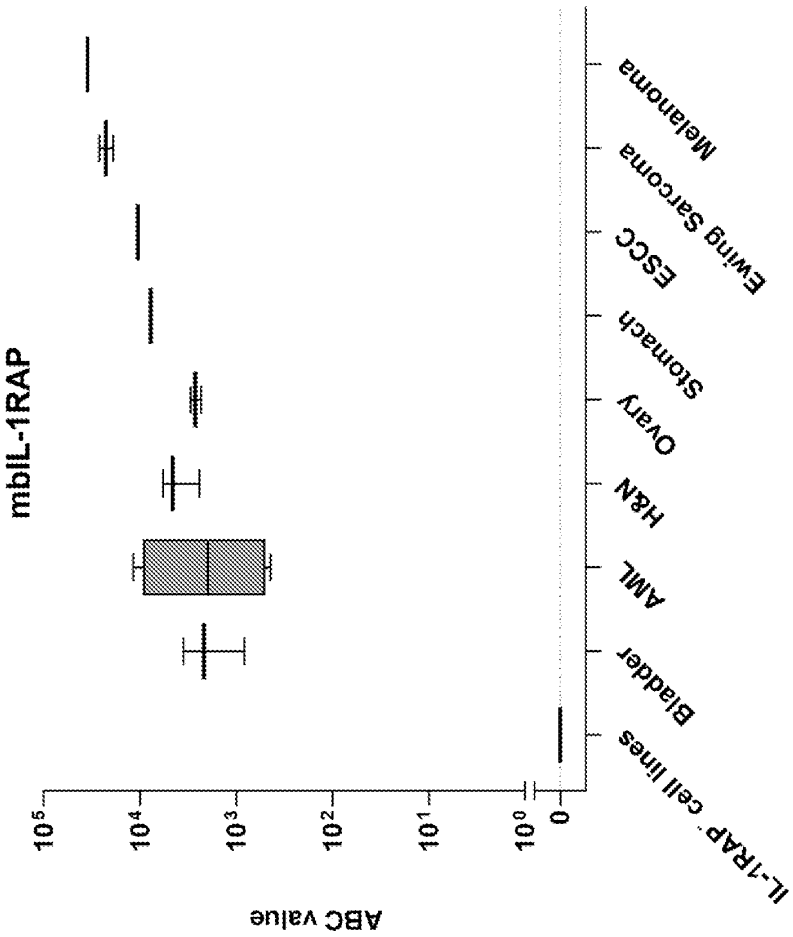

mbIL-1RAP
ABC value
10^5
10^4
10^3
10^2
10^1
10^0
0
IL-1RAP- cell lines
Bladder
AML
H&N
Ovary
Stomach
ESCC
Ewing Sarcoma
Melanoma

FIG. 8

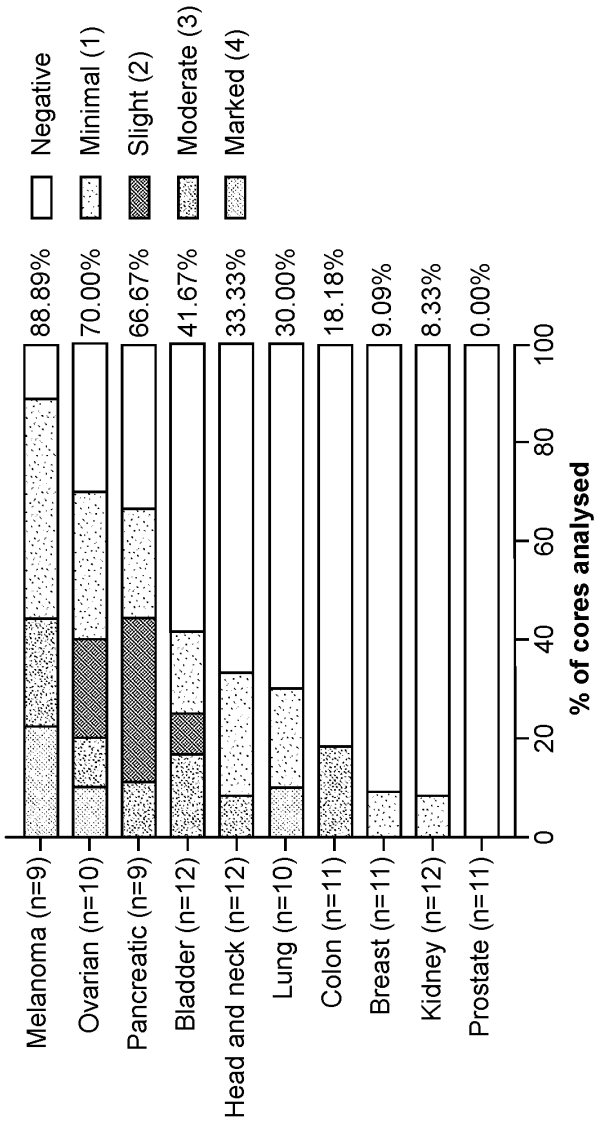

Negative
Minimal (1)
Slight (2)
Moderate (3)
Marked (4)
88.89%
70.00%
66.67%
41.67%
33.33%
30.00%
18.18%
9.09%
8.33%
0.00%
Melanoma (n=9)
Ovarian (n=10)
Pancreatic (n=9)
Bladder (n=12)
Head and neck (n=12)
Lung (n=10)
Colon (n=11)
Breast (n=11)
Kidney (n=12)
Prostate (n=11)
0
20
40
60
80
100
% of cores analysed

FIG. 9

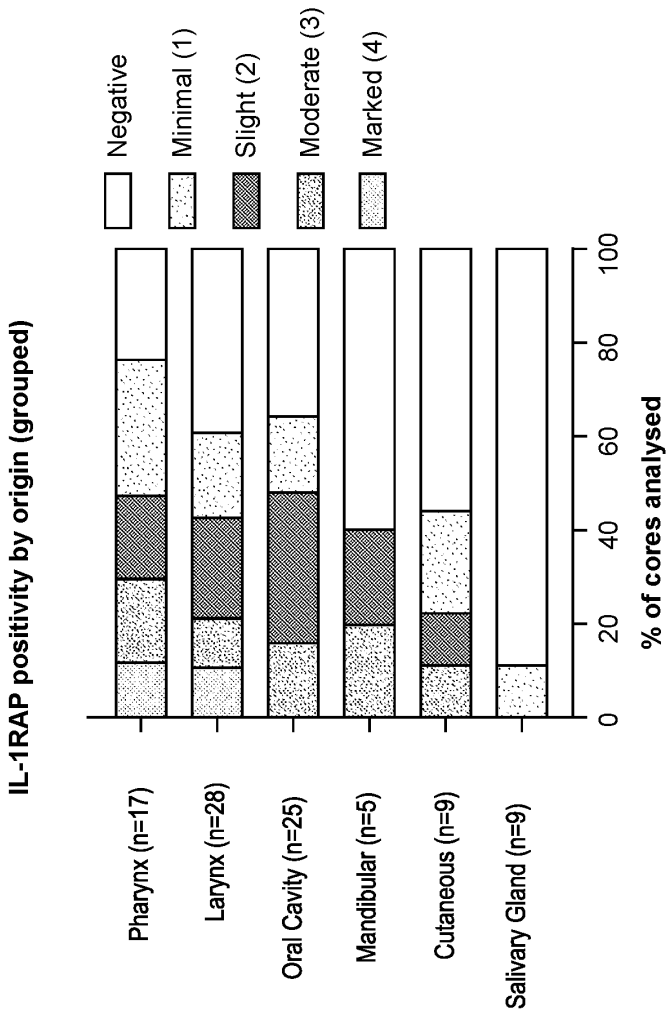

IL-1RAP positivity by origin (grouped)
Negative
Minimal (1)
Slight (2)
Moderate (3)
Marked (4)
Pharynx (n=17)
Larynx (n=28)
Oral Cavity (n=25)
Mandibular (n=5)
Cutaneous (n=9)
Salivary Gland (n=9)
0
20
40
60
80
100
% of cores analysed

FIG. 10A

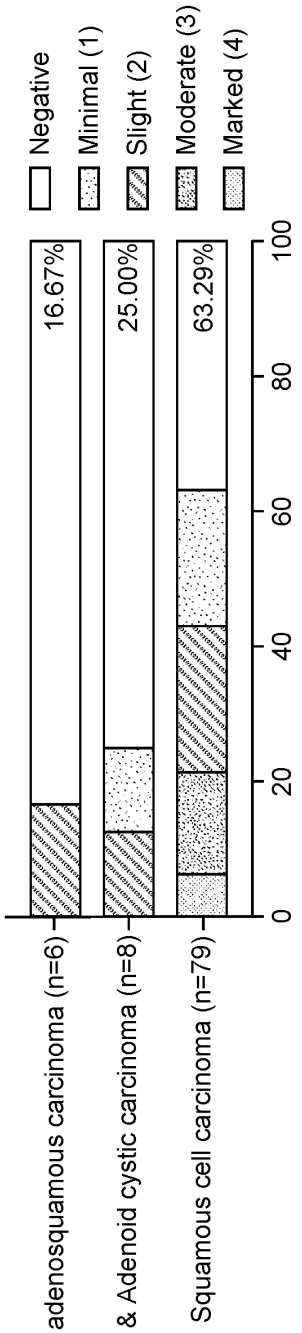


FIG. 10B

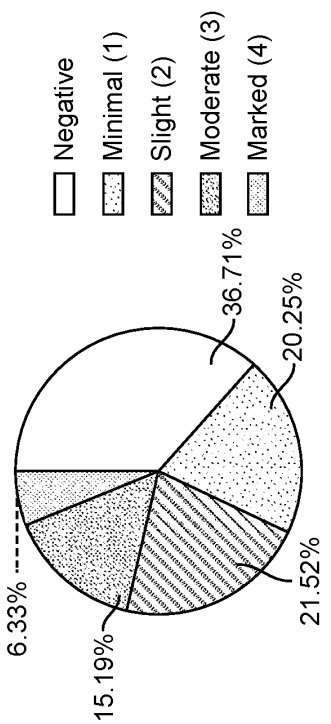


FIG. 10C

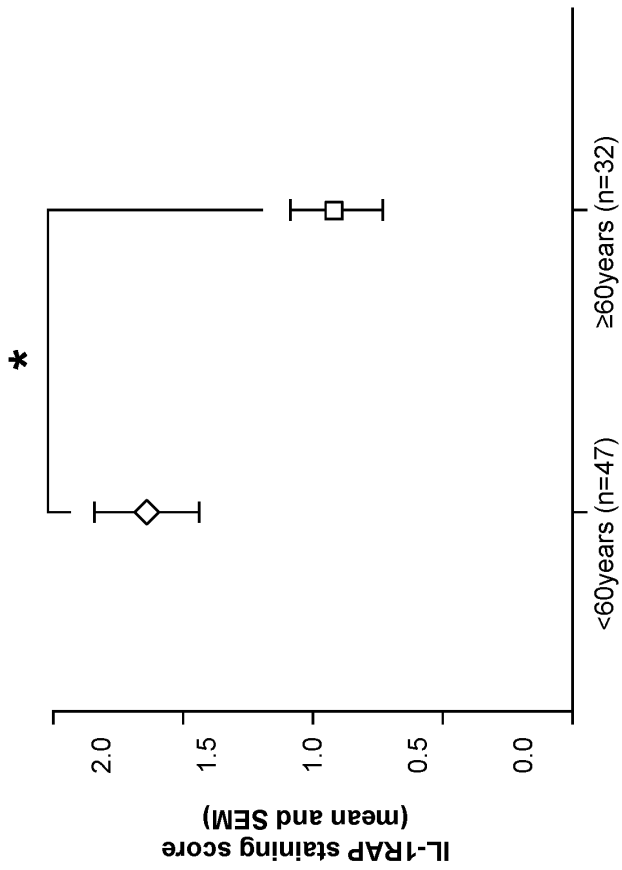
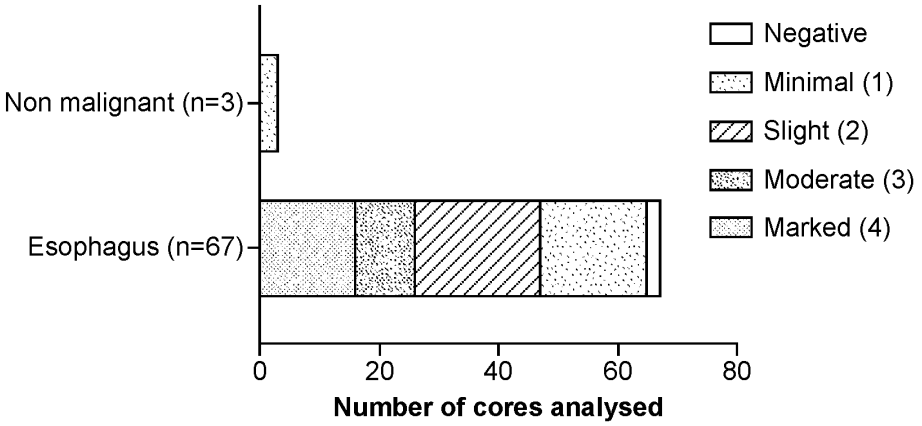

IL-1RAP staining score
(mean and SEM)
2.0
1.5
1.0
0.5
0.0
*
<60years (n=47)
≥60years (n=32)

FIG. 10D


Non malignant (n=3)
Esophagus (n=67)
0
20
40
60
80
Number of cores analysed
Negative
Minimal (1)
Slight (2)
Moderate (3)
Marked (4)

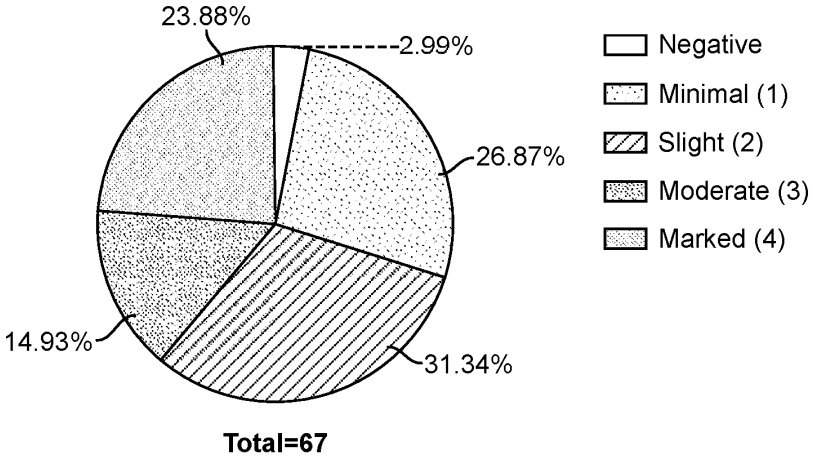

23.88%
2.99%
26.87%
14.93%
31.34%
Total=67
Negative
Minimal (1)
Slight (2)
Moderate (3)
Marked (4)

FIG. 11

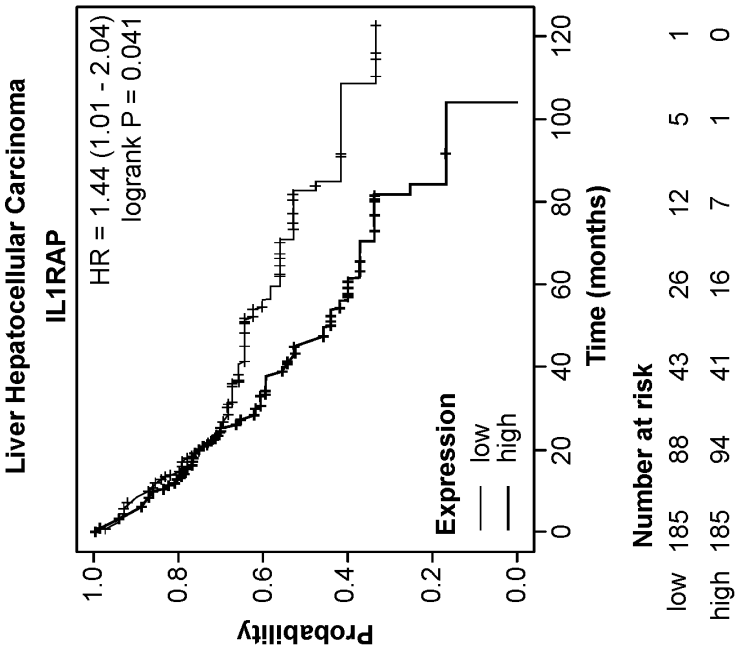


FIG. 12B

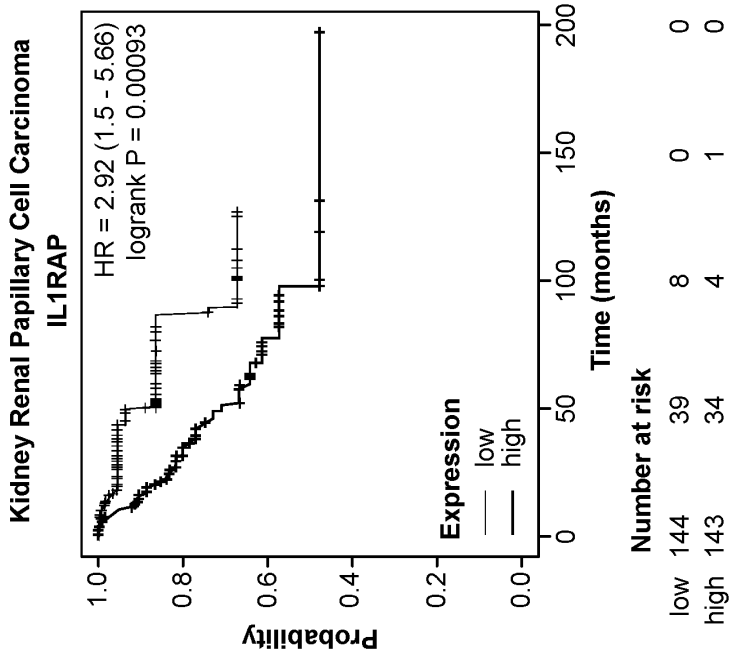


FIG. 12A

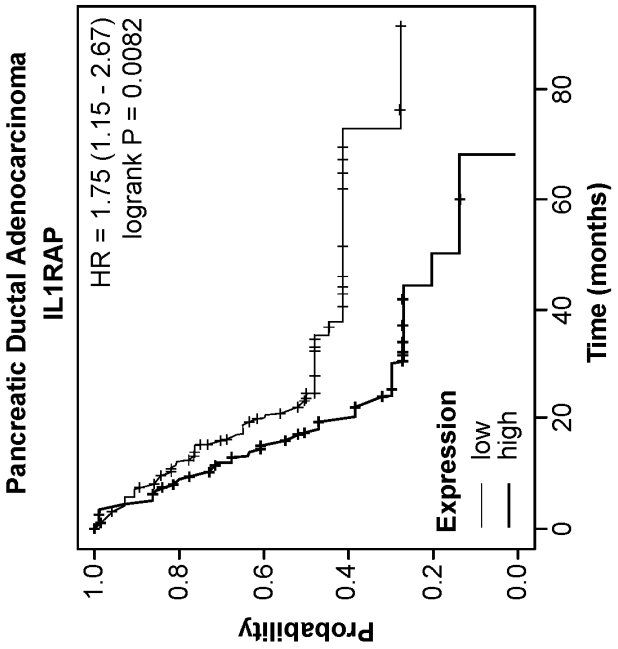


FIG. 12D

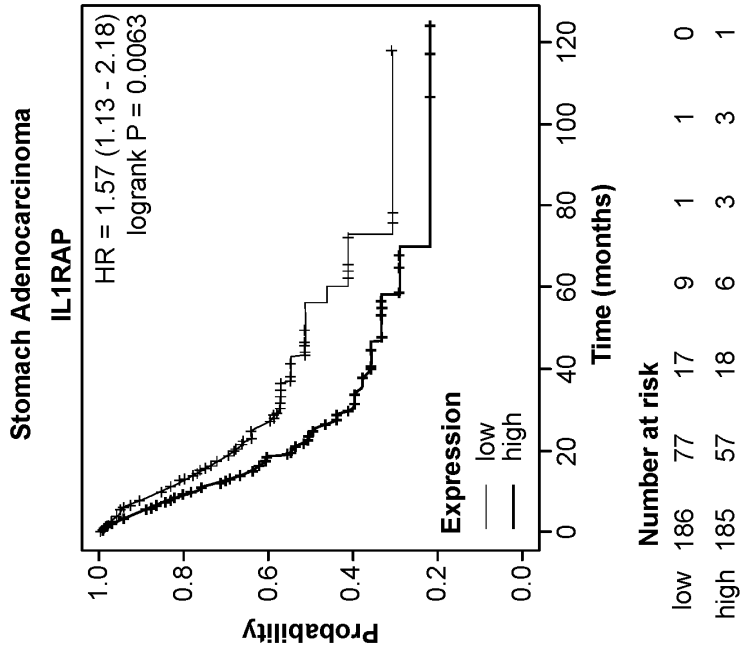


FIG. 12C

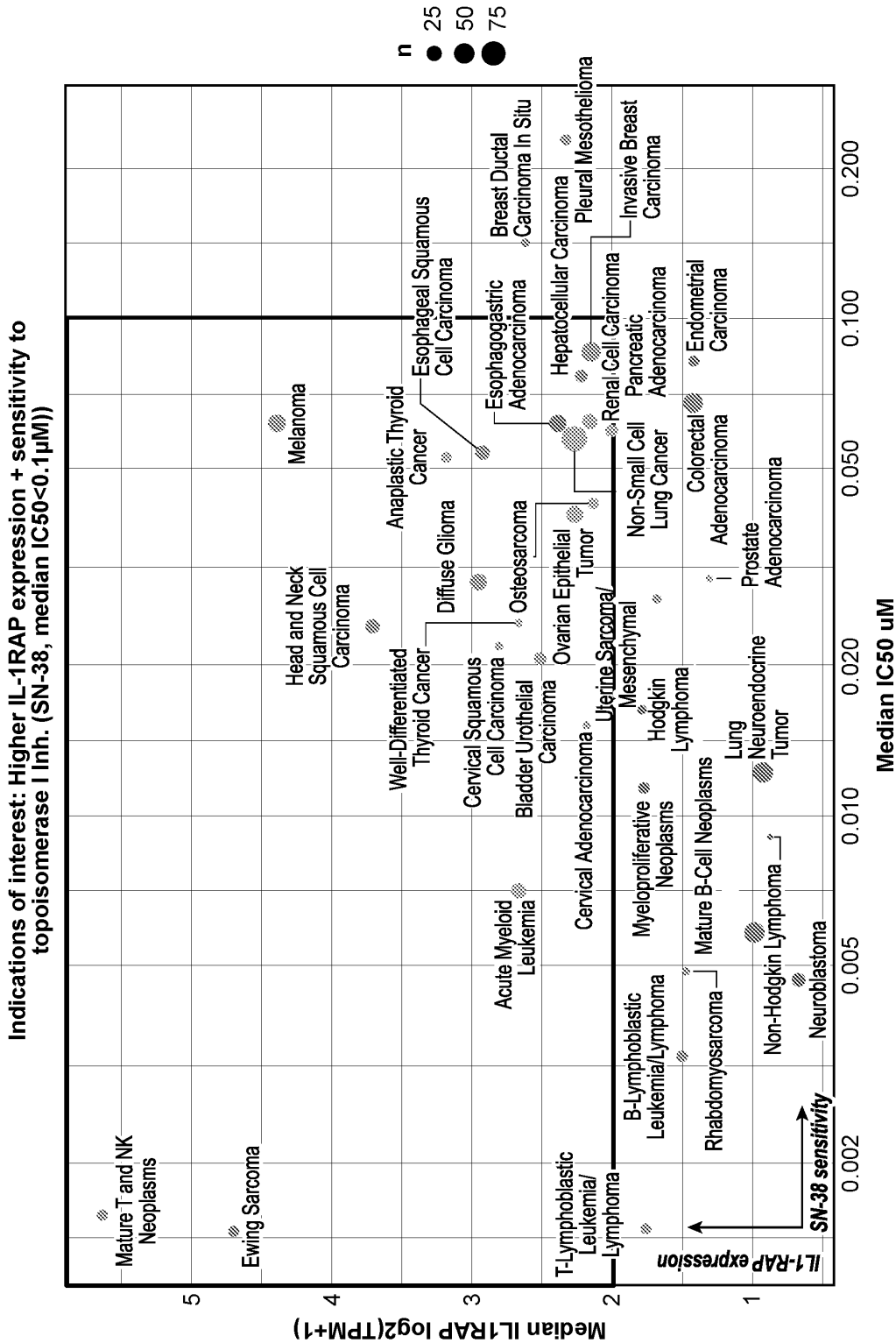

Indications of interest: Higher IL-1RAP expression + sensitivity to topoisomerase I Inh. (SN-38, median IC50<0.1μM))
Median IL1RAP log2(TPM+1)
Median IC50 uM
n
25
50
75
IL1-RAP expression
SN-38 sensitivity
Mature T and NK Neoplasms
Ewing Sarcoma
T-Lymphoblastic Leukemia/ Lymphoma
B-Lymphoblastic Leukemia/Lymphoma
Rhabdomyosarcoma
Neuroblastoma
Non-Hodgkin Lymphoma
Acute Myeloid Leukemia
Myeloproliferative Neoplasms
Mature B-Cell Neoplasms
Cervical Adenocarcinoma
Bladder Urothelial Carcinoma
Cervical Squamous Cell Carcinoma
Lung Neuroendocrine Tumor
Hodgkin Lymphoma
Uterine Sarcoma/ Mesenchymal
Ovarian Epithelial Tumor
Osteosarcoma
Diffuse Glioma
Well-Differentiated Thyroid Cancer
Head and Neck Squamous Cell Carcinoma
Melanoma
Anaplastic Thyroid Cancer
Esophageal Squamous Cell Carcinoma
Esophagogastric Adenocarcinoma
Hepatocellular Carcinoma
Renal Cell Carcinoma
Non-Small Cell Lung Cancer
Prostate Adenocarcinoma
Colorectal Adenocarcinoma
Pancreatic Adenocarcinoma
Endometrial Carcinoma
Breast Ductal Carcinoma In Situ
Pleural Mesothelioma
Invasive Breast Carcinoma

FIG. 13

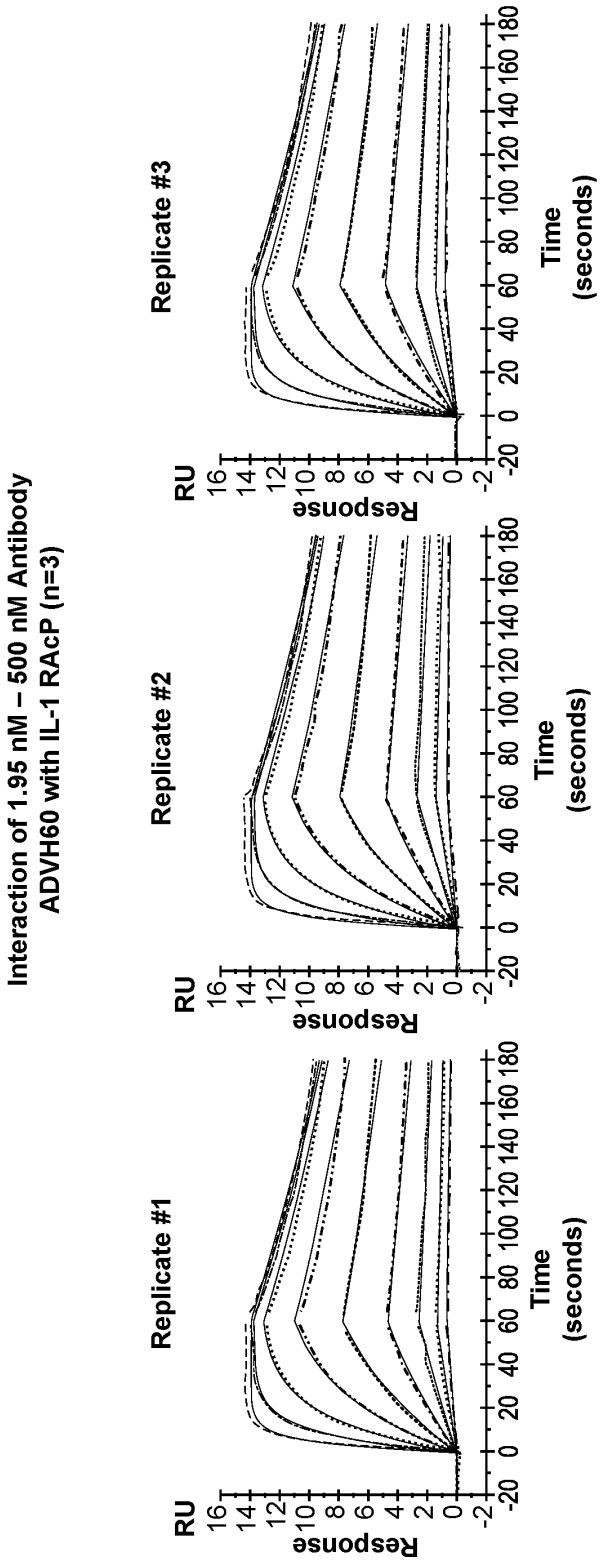

Interaction of 1.95 nM – 500 nM Antibody
ADVH60 with IL-1 RAcP (n=3)
Replicate #1
Replicate #2
Replicate #3
Response
RU
Time
(seconds)

FIG. 14

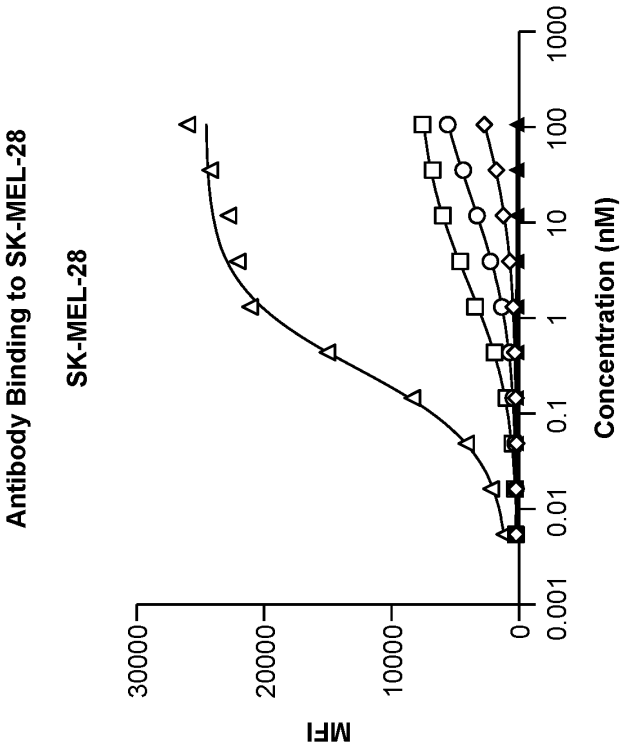

Antibody Binding to SK-MEL-28
SK-MEL-28
MFI
30000
20000
10000
0
0.001
0.01
0.1
1
10
100
1000
Concentration (nM)

FIG. 15

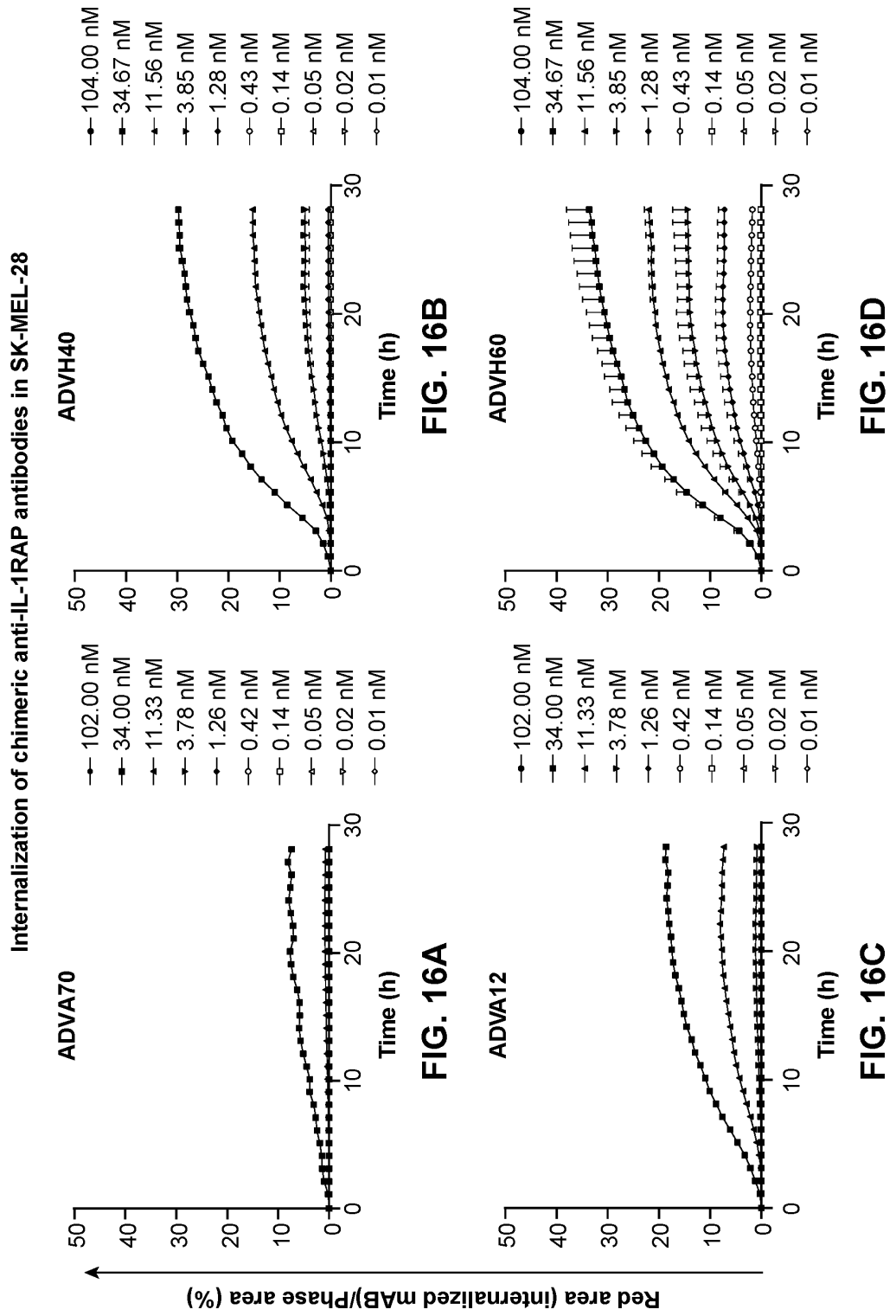


FIG. 16A

FIG. 16B

FIG. 16C

FIG. 16D

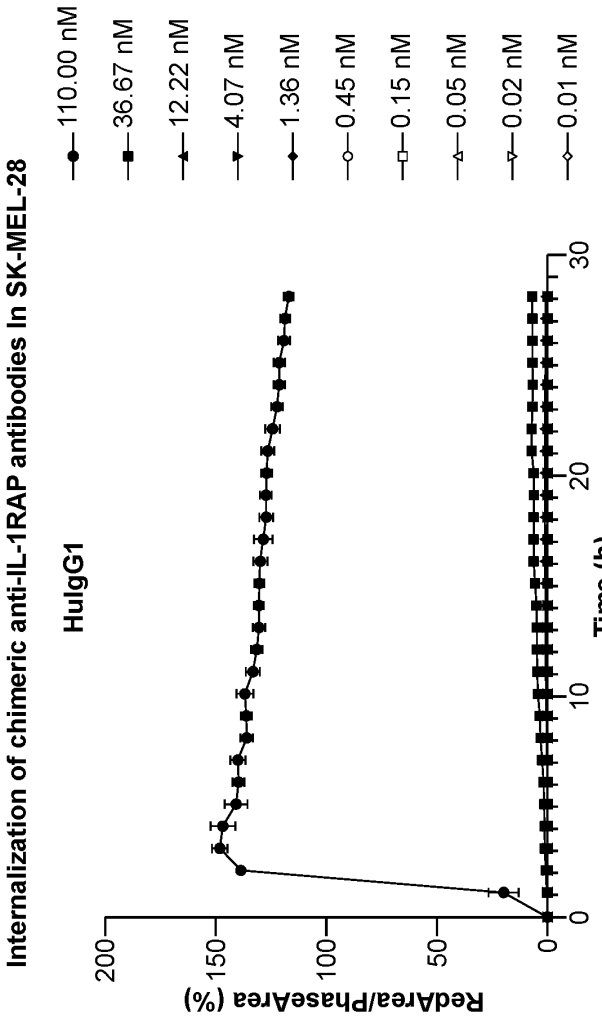

Internalization of chimeric anti-IL-1RAP antibodies In SK-MEL-28
HuIgG1
110.00 nM
36.67 nM
12.22 nM
4.07 nM
1.36 nM
0.45 nM
0.15 nM
0.05 nM
0.02 nM
0.01 nM
RedArea/PhaseArea (%)
200
150
100
50
0
0
10
20
30
Time (h)

FIG. 16E

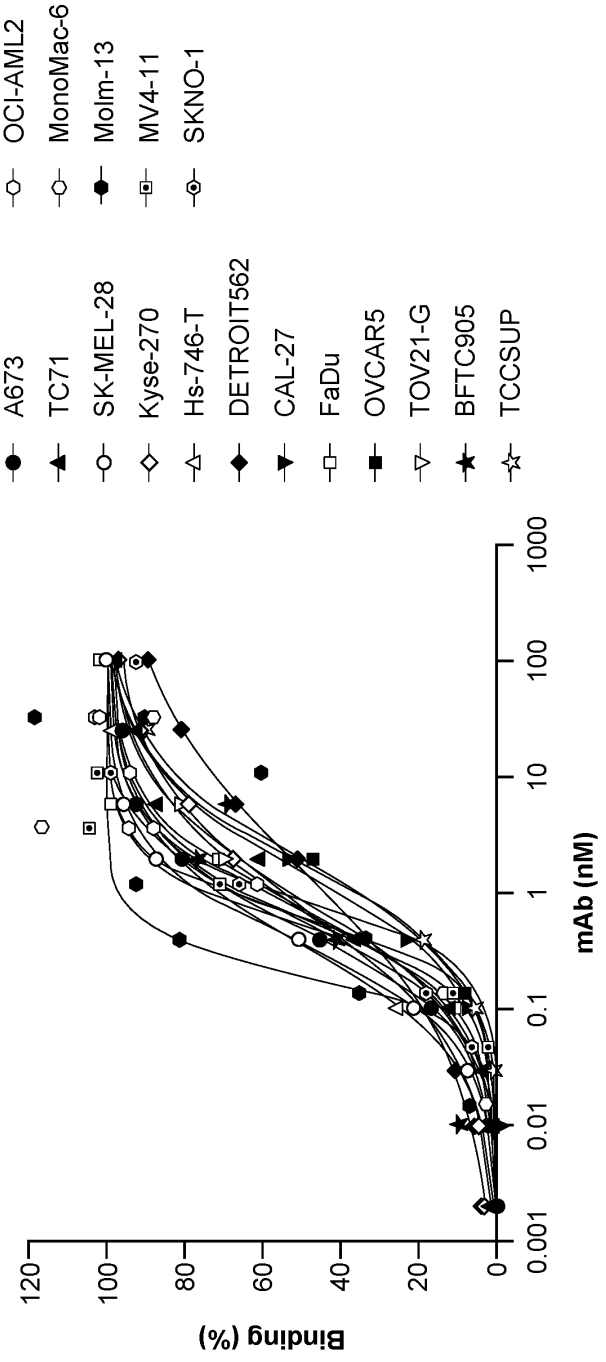

A673
TC71
SK-MEL-28
Kyse-270
Hs-746-T
DETROIT562
CAL-27
FaDu
OVCAR5
TOV21-G
BFTC905
TCCSUP
OCI-AML2
MonoMac-6
Molm-13
MV4-11
SKNO-1
Binding (%)
120
100
80
60
40
20
0
0.001
0.01
0.1
1
10
100
1000
mAb (nM)

FIG. 17A

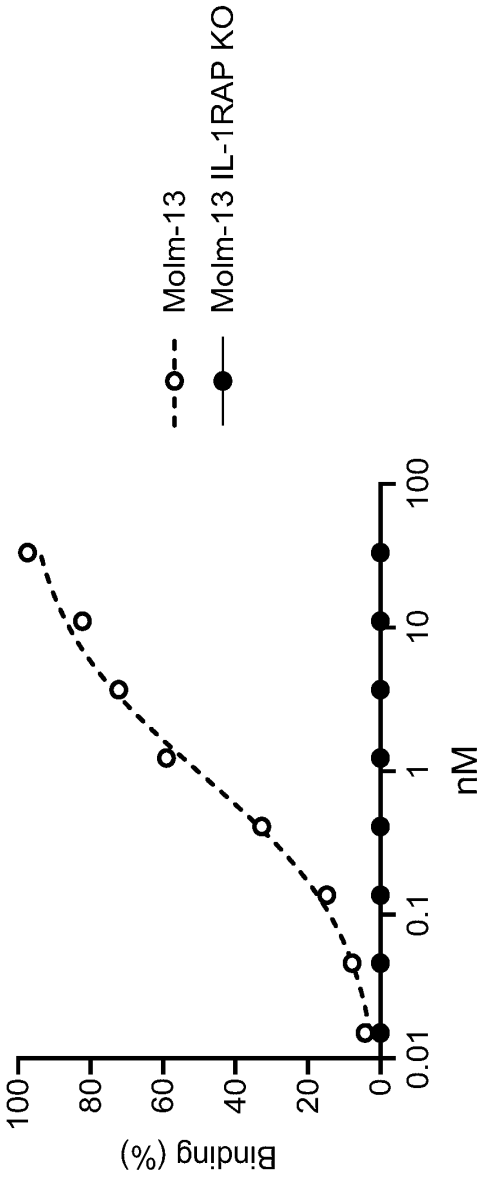

Molm-13
Molm-13 IL-1RAP KO
Binding (%)
0
20
40
60
80
100
0.01
0.1
1
10
100
nM

FIG. 17B

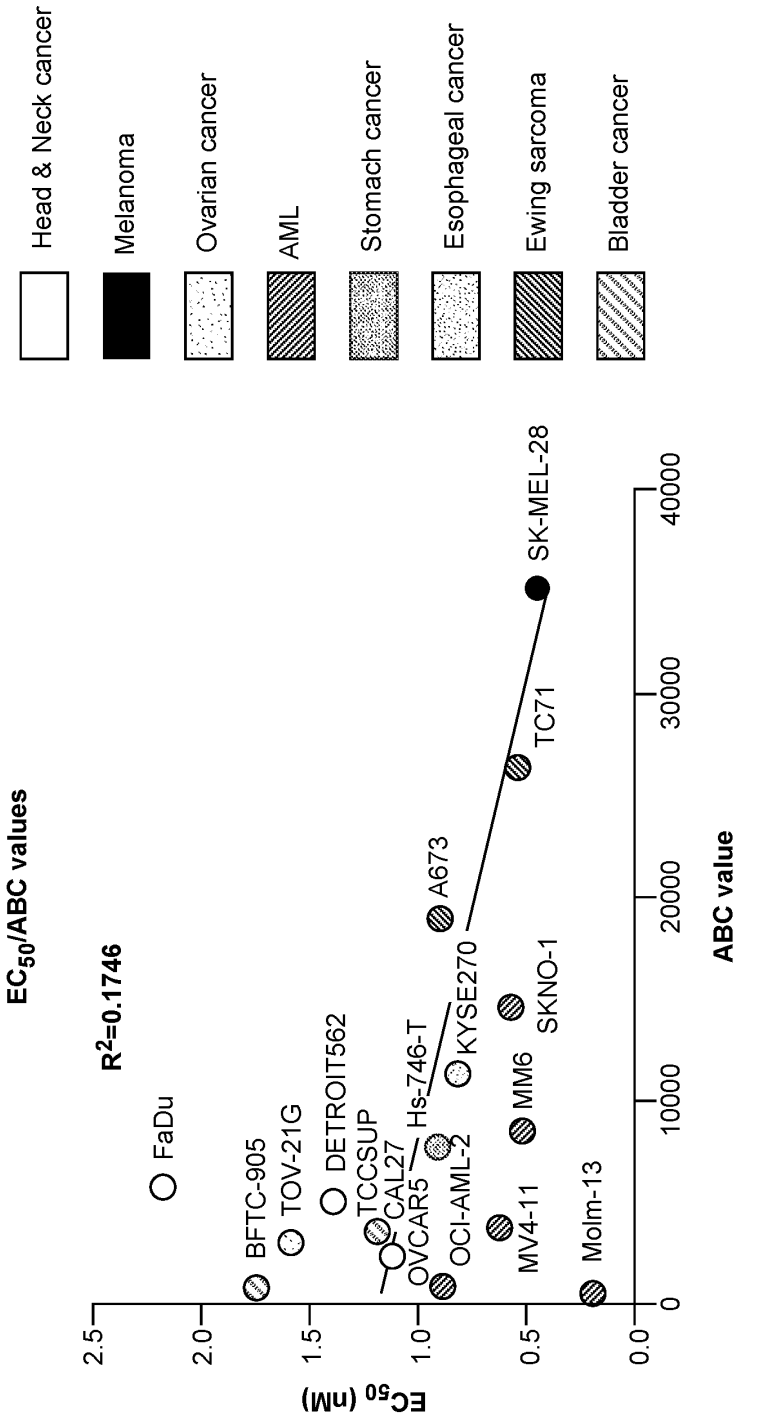

Head & Neck cancer
Melanoma
Ovarian cancer
AML
Stomach cancer
Esophageal cancer
Ewing sarcoma
Bladder cancer
EC50/ABC values
R2=0.1746
FaDu
BFTC-905
TOV-21G
DETROIT562
TCCSUP
CAL27
OVCAR5
Hs-746-T
OCI-AML-2
KYSE270
A673
MV4-11
MM6
SKNO-1
TC71
SK-MEL-28
Molm-13
EC50 (nM)
ABC value
0.0
0.5
1.0
1.5
2.0
2.5
0
10000
20000
30000
40000

FIG. 18

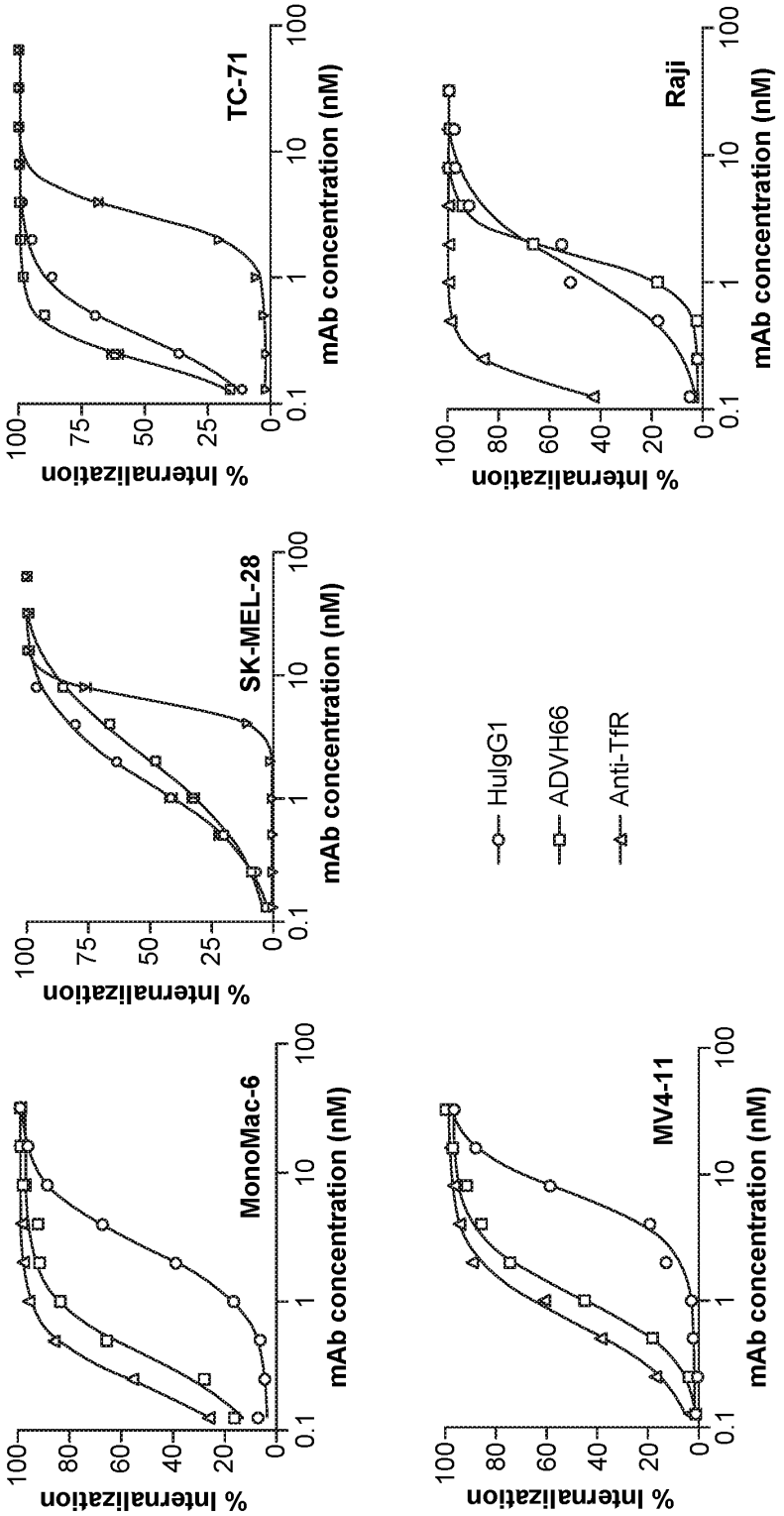

TC-71
SK-MEL-28
MonoMac-6
Raji
MV4-11
% Internalization
mAb concentration (nM)
0.1
1
10
100
0
25
50
75
20
40
60
80
HuIgG1
ADVH66
Anti-TfR

FIG. 19

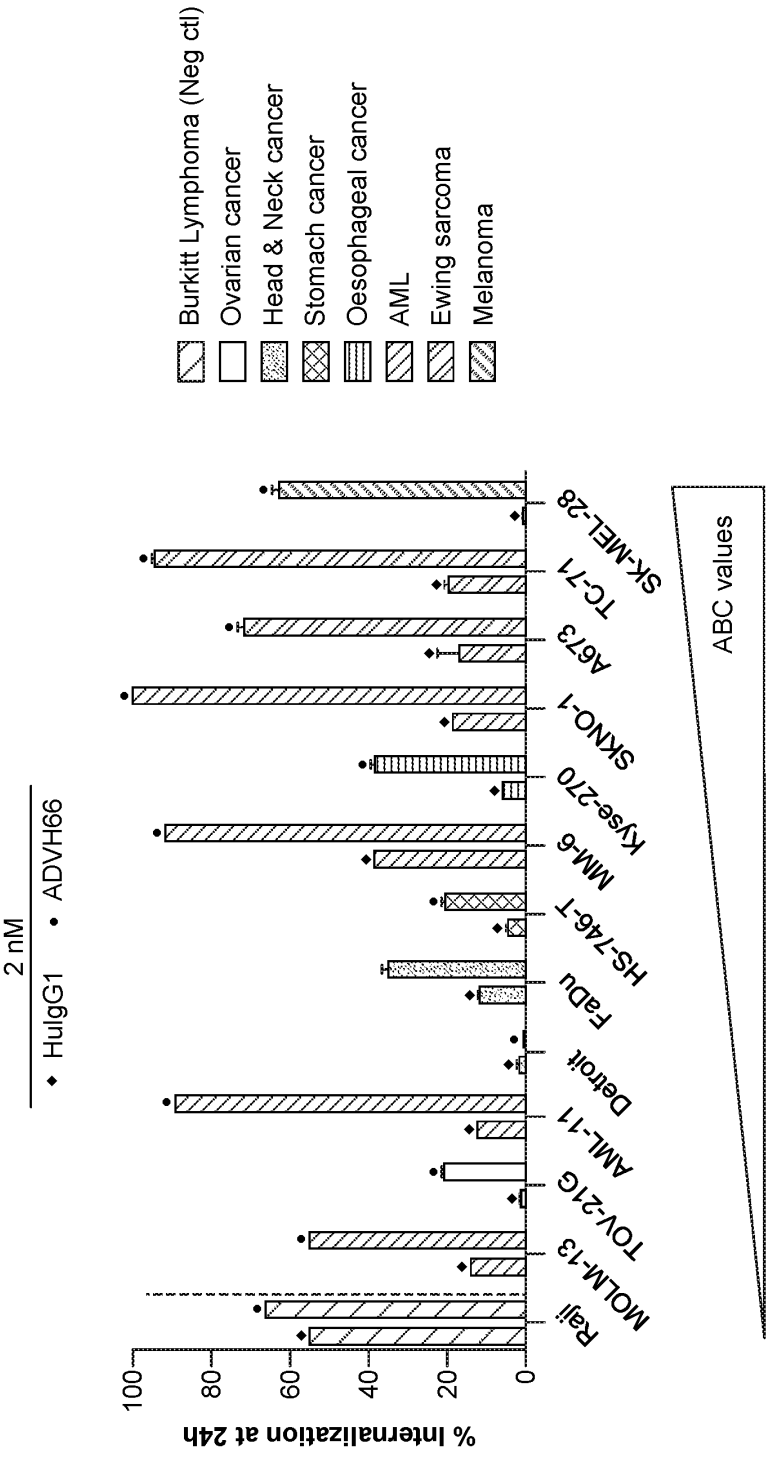

Burkitt Lymphoma (Neg ctl)
Ovarian cancer
Head & Neck cancer
Stomach cancer
Oesophageal cancer
AML
Ewing sarcoma
Melanoma
2 nM
HulgG1
ADVH66
% Internalization at 24h
100
80
60
40
20
0
Raji
MOLM-13
TOV-21G
AML-11
Detroit
FaDu
HS-746-T
MM-6
Kyse-270
SKNO-1
A673
TC-71
SK-MEL-28
ABC values

FIG. 20

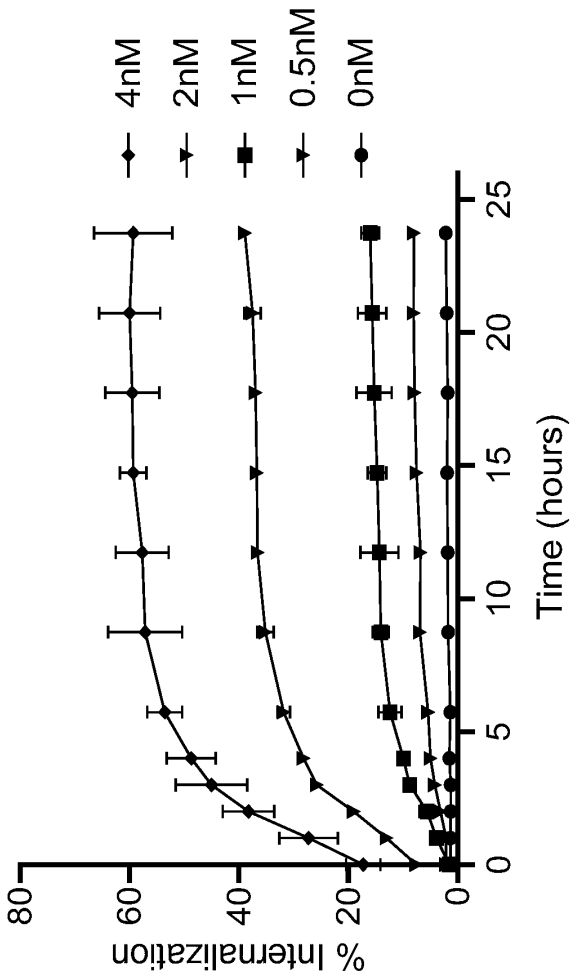

4nM
2nM
1nM
0.5nM
0nM
% Internalization
0
20
40
60
80
0
5
10
15
20
25
Time (hours)

FIG. 21

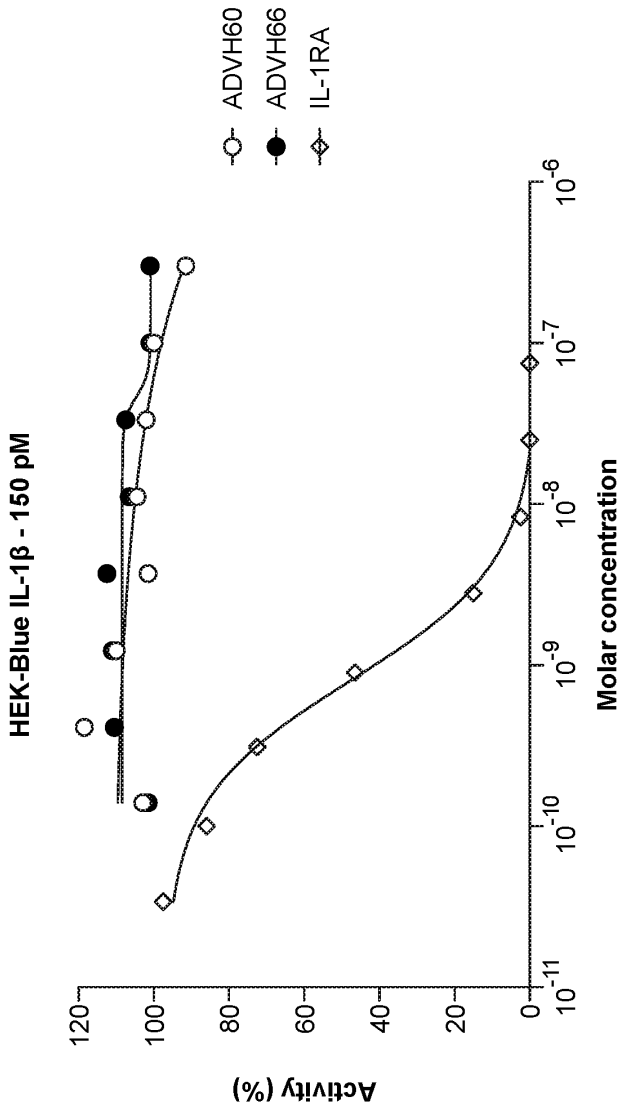

HEK-Blue IL-1β - 150 pM
ADVH60
ADVH66
IL-1RA
Activity (%)
120
100
80
60
40
20
0
Molar concentration
10-6
10-7
10-8
10-9
10-10
10-11

FIG. 22

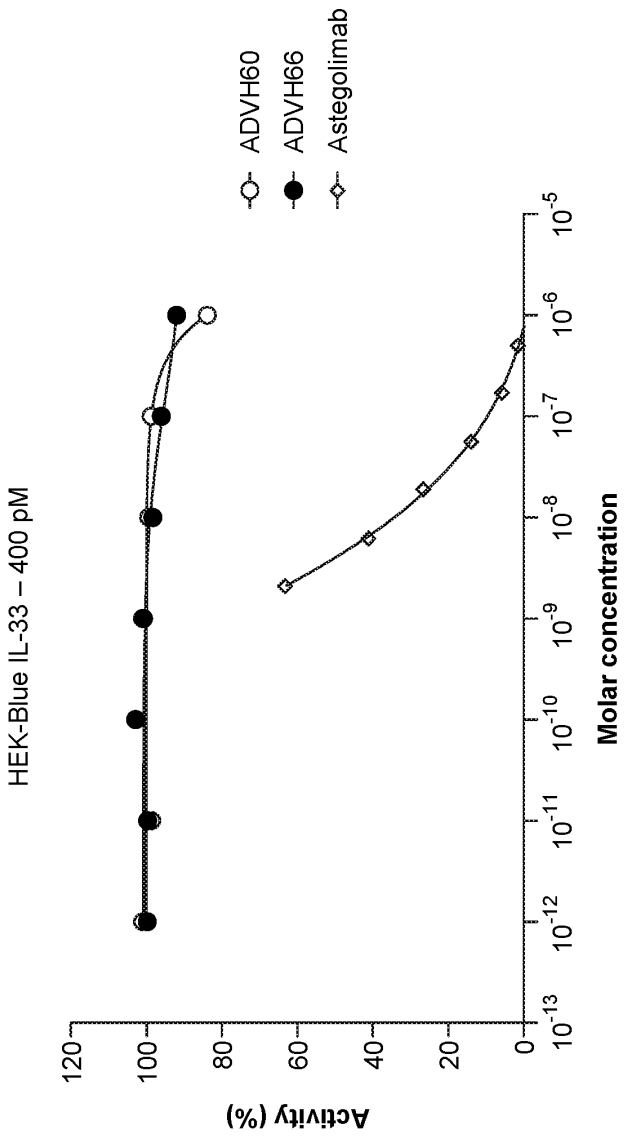

HEK-Blue IL-33 – 400 pM
ADVH60
ADVH66
Astegolimab
Activity (%)
120
100
80
60
40
20
0
Molar concentration
10-13
10-12
10-11
10-10
10-9
10-8
10-7
10-6
10-5

FIG. 23

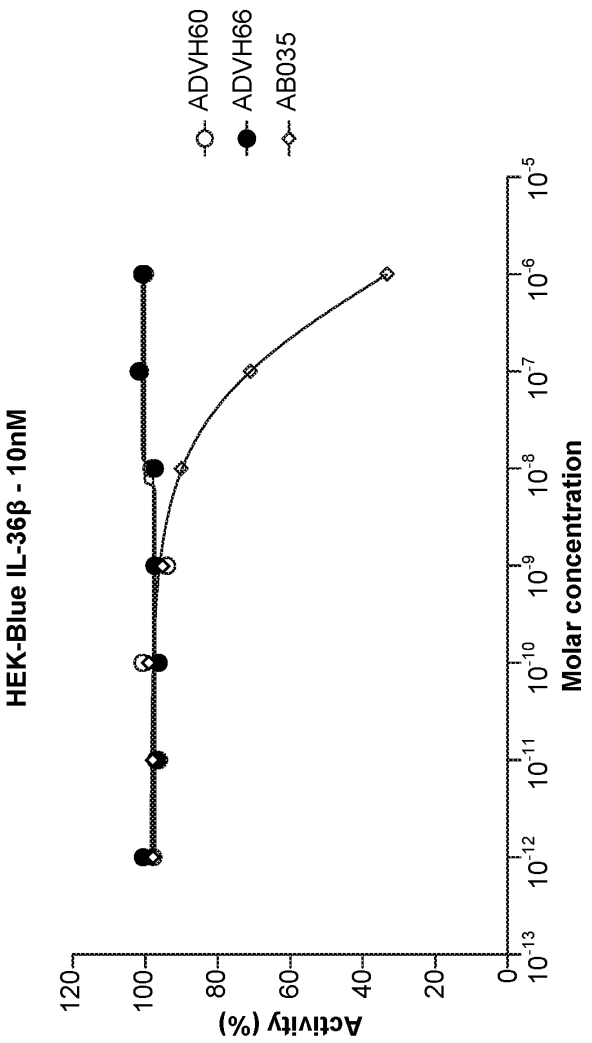

HEK-Blue IL-36β - 10nM
ADVH60
ADVH66
AB035
Activity (%)
120
100
80
60
40
20
0
Molar concentration
10-13
10-12
10-11
10-10
10-9
10-8
10-7
10-6
10-5

FIG. 24

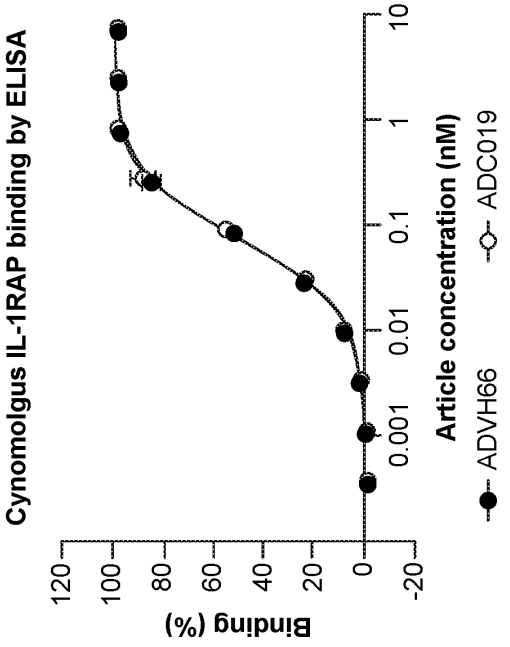


FIG. 25B

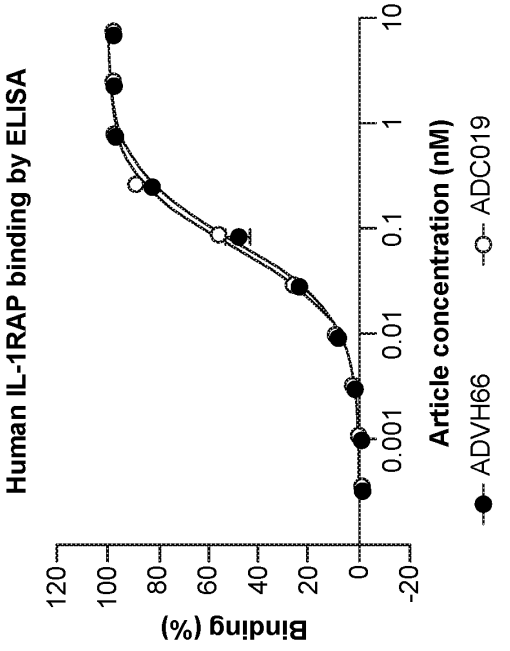


FIG. 25A

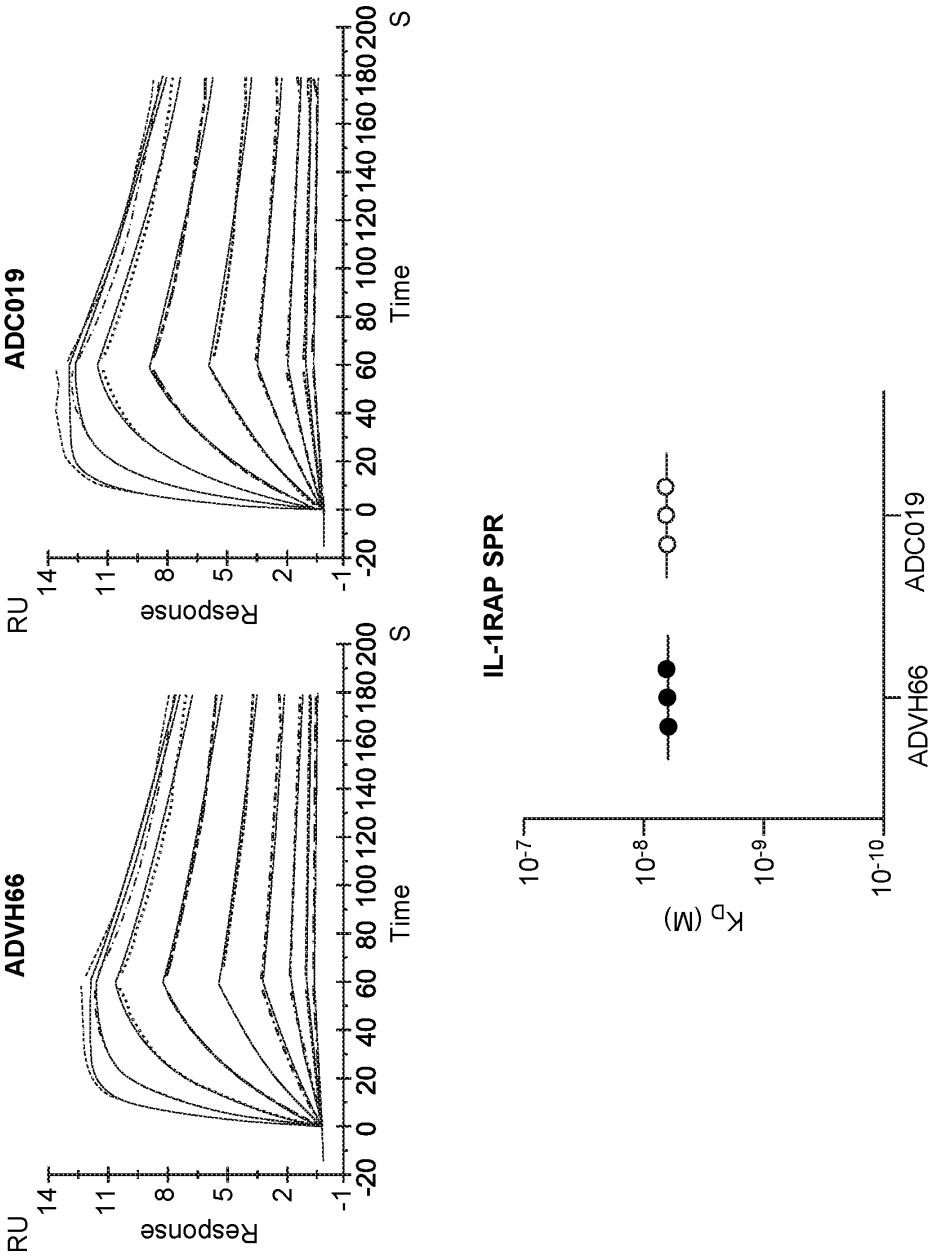

ADVH66
ADC019
RU
Response
Time
S
IL-1RAP SPR
K_D (M)
ADVH66
ADC019

FIG. 26

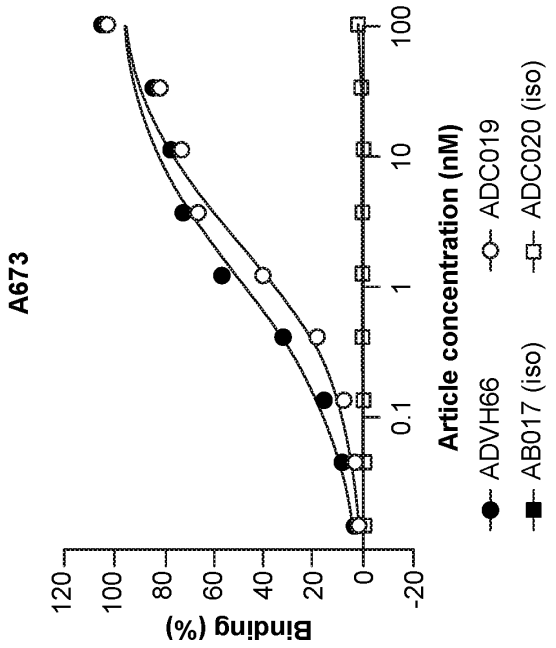


FIG. 27B

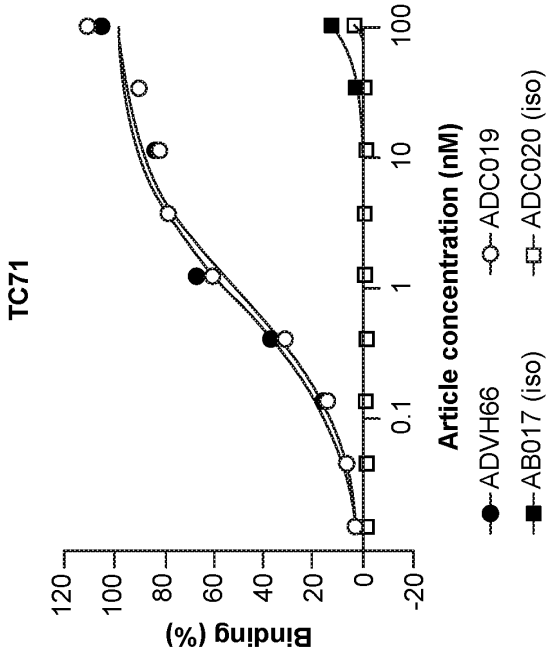


FIG. 27A

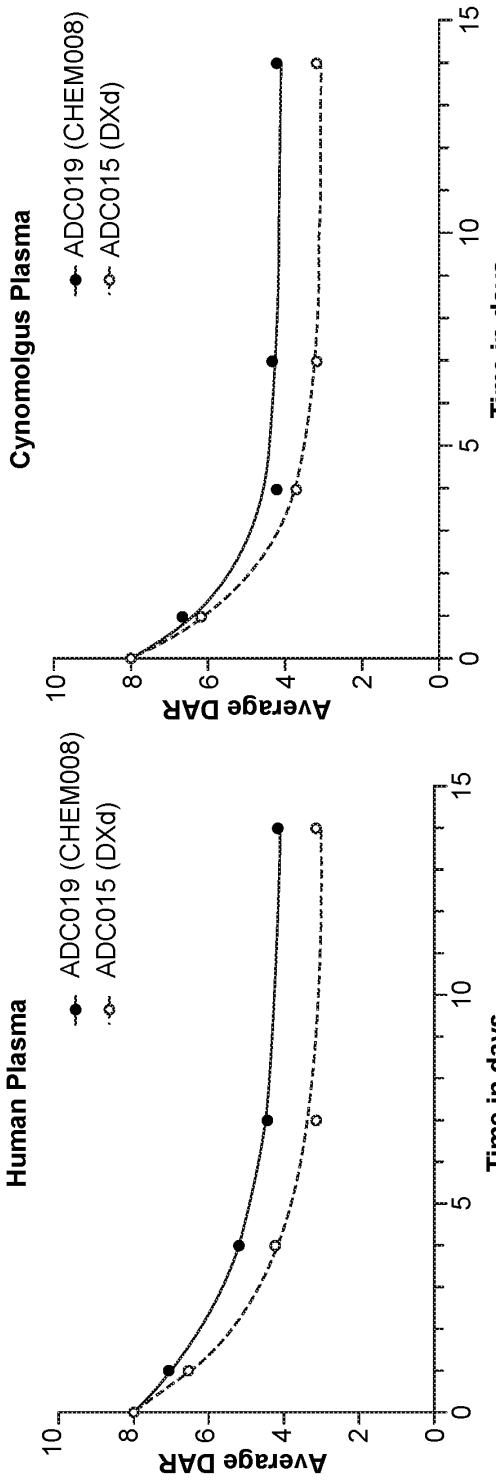


FIG. 28A

FIG. 28B

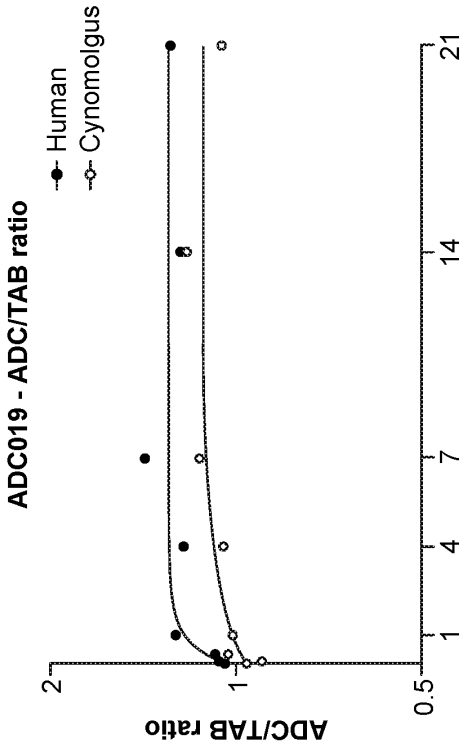

ADC019 - ADC/TAB ratio
Human
Cynomolgus
ADC/TAB ratio
2
1
0.5
1
4
7
14
21
Time in days

FIG. 29

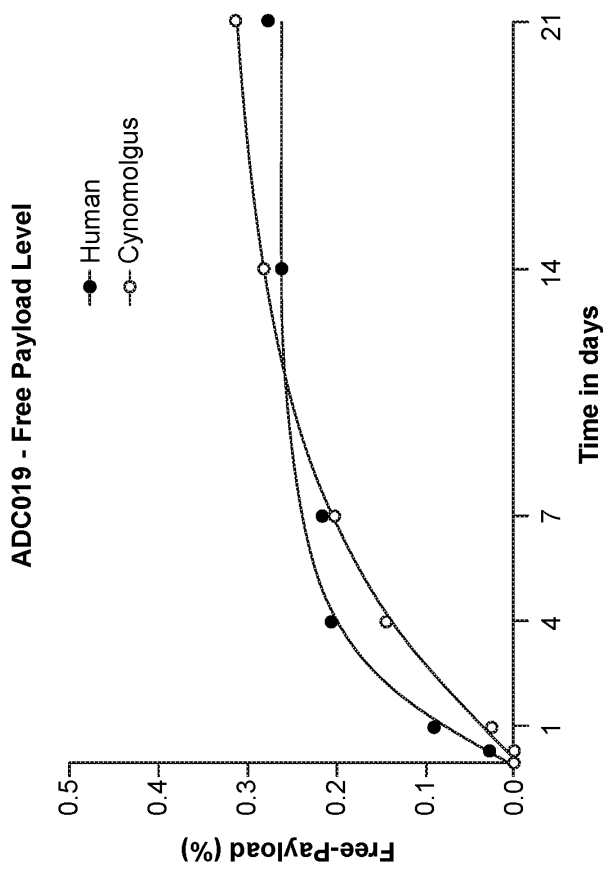

ADC019 - Free Payload Level
Human
Cynomolgus
Free-Payload (%)
0.0
0.1
0.2
0.3
0.4
0.5
1
4
7
14
21
Time in days

FIG. 30

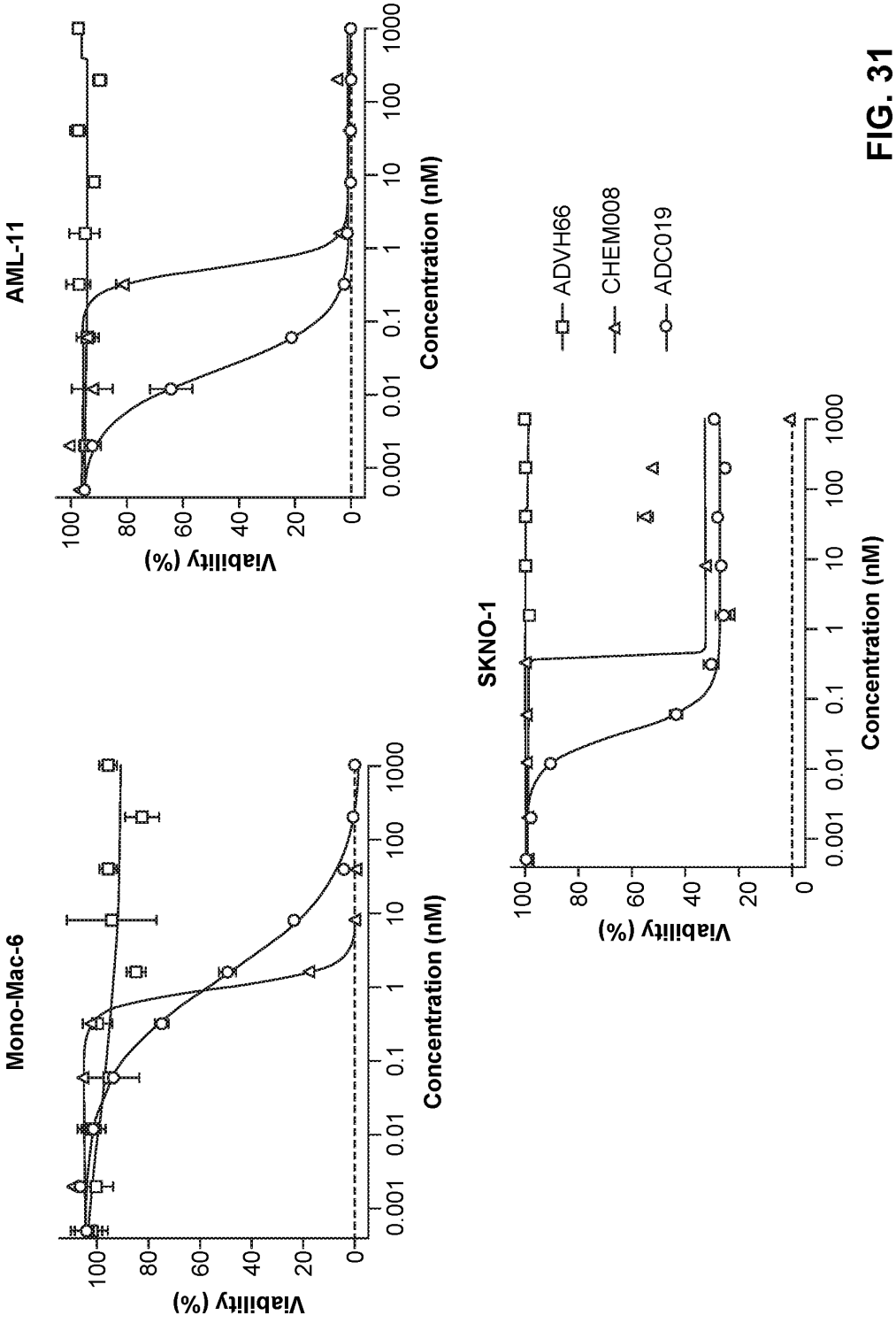

AML-11
Viability (%)
Concentration (nM)
Mono-Mac-6
Viability (%)
Concentration (nM)
SKNO-1
Viability (%)
Concentration (nM)
ADVH66
CHEM008
ADC019

FIG. 31

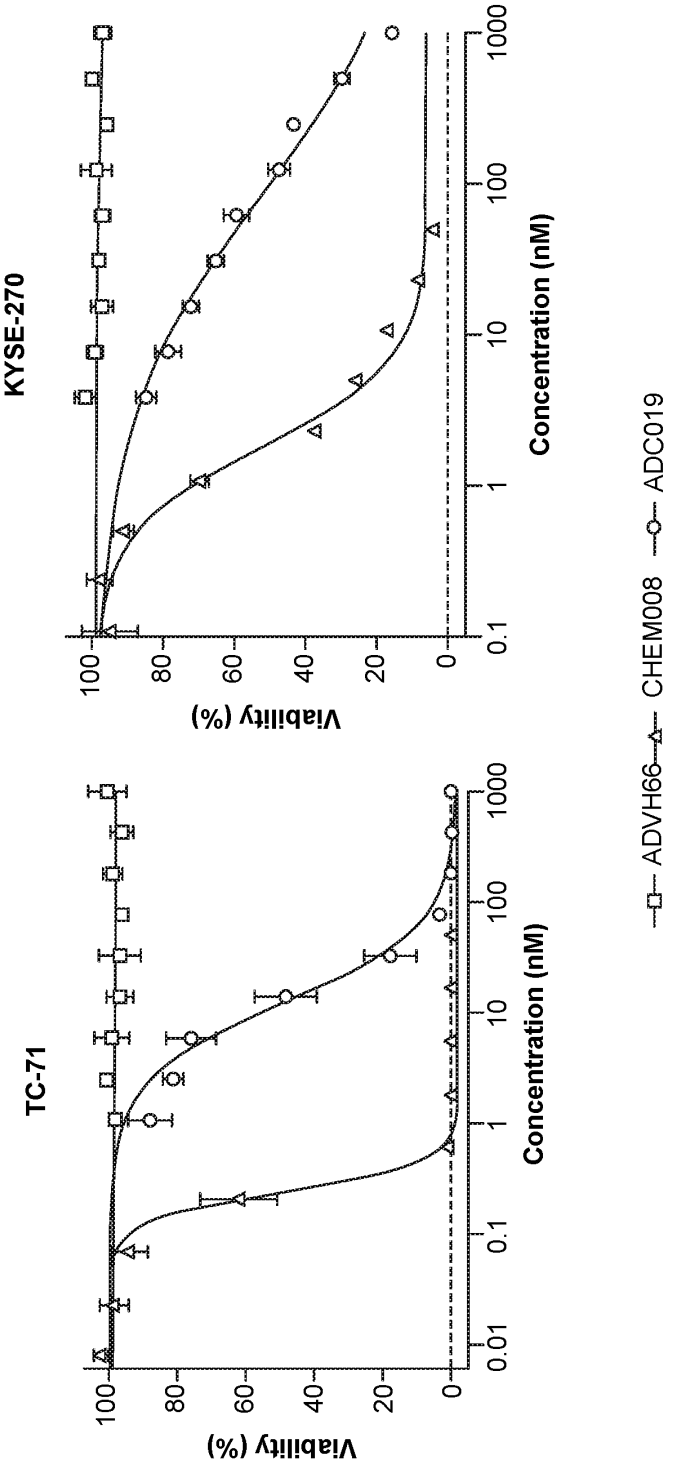

KYSE-270
TC-71
Viability (%)
Concentration (nM)
0
20
40
60
80
100
0.01
0.1
1
10
100
1000
ADVH66
CHEM008
ADC019

FIG. 31 (Cont.)

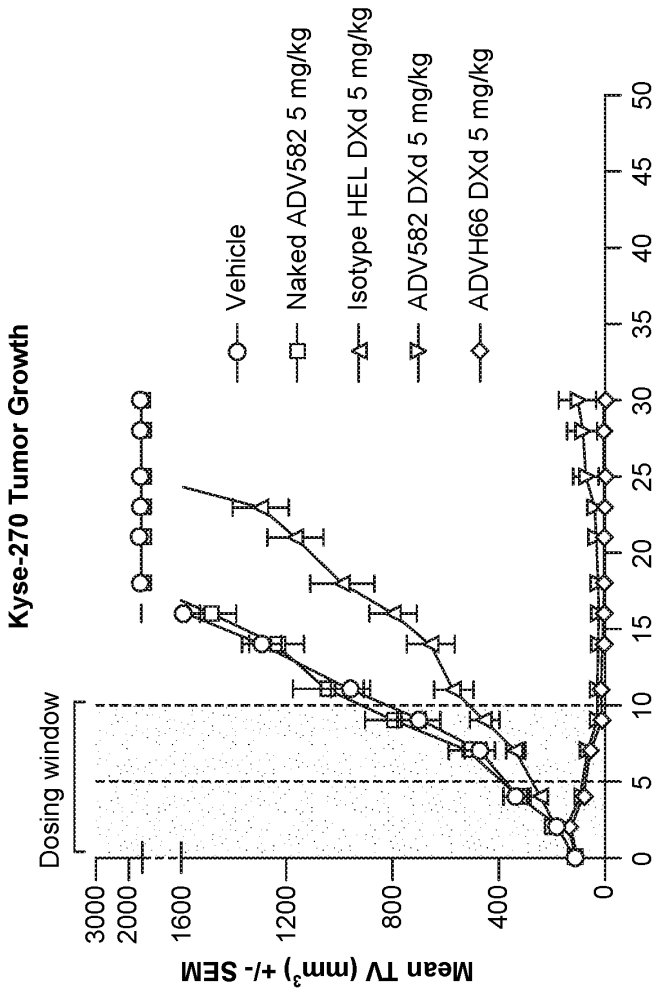

Kyse-270 Tumor Growth
Dosing window
Vehicle
Naked ADV582 5 mg/kg
Isotype HEL DXd 5 mg/kg
ADV582 DXd 5 mg/kg
ADVH66 DXd 5 mg/kg
Mean TV (mm3) +/- SEM
3000
2000
1600
1200
800
400
0
0
5
10
15
20
25
30
35
40
45
50
Time (days)

FIG. 32A

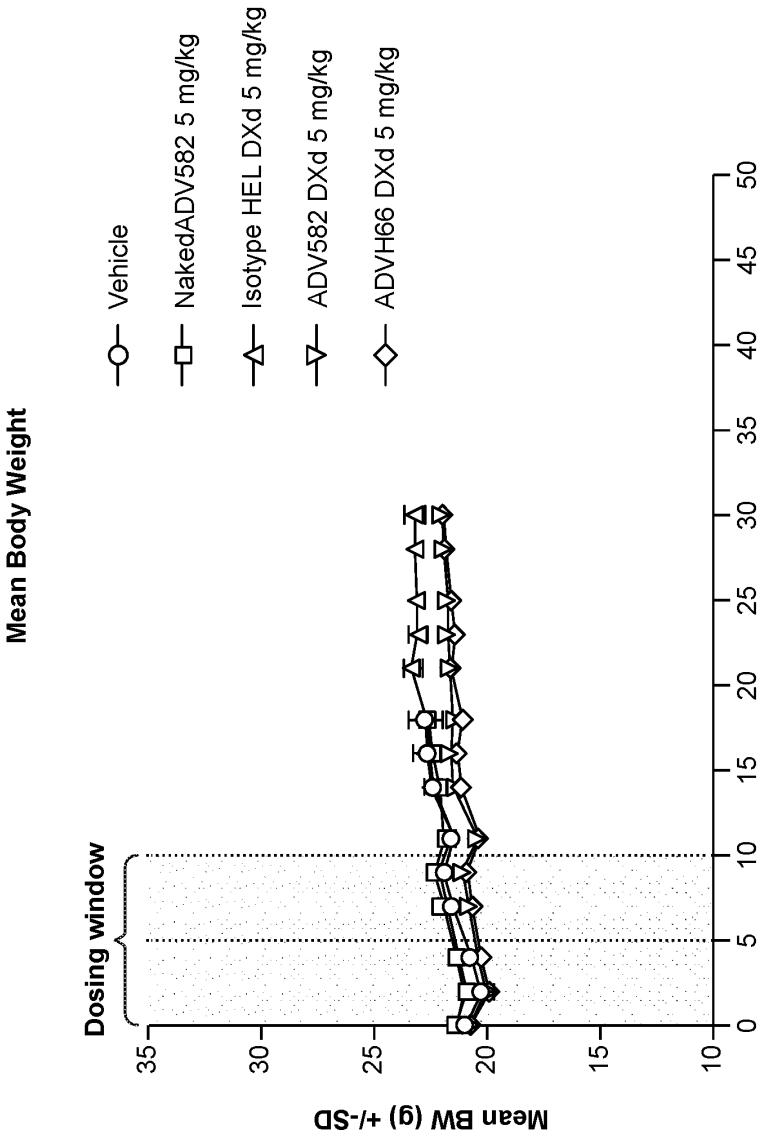

Mean Body Weight
Vehicle
NakedADV582 5 mg/kg
Isotype HEL DXd 5 mg/kg
ADV582 DXd 5 mg/kg
ADVH66 DXd 5 mg/kg
Dosing window
Mean BW (g) +/-SD
Time (days)
35
30
25
20
15
10
0
5
10
15
20
25
30
35
40
45
50

FIG. 32B

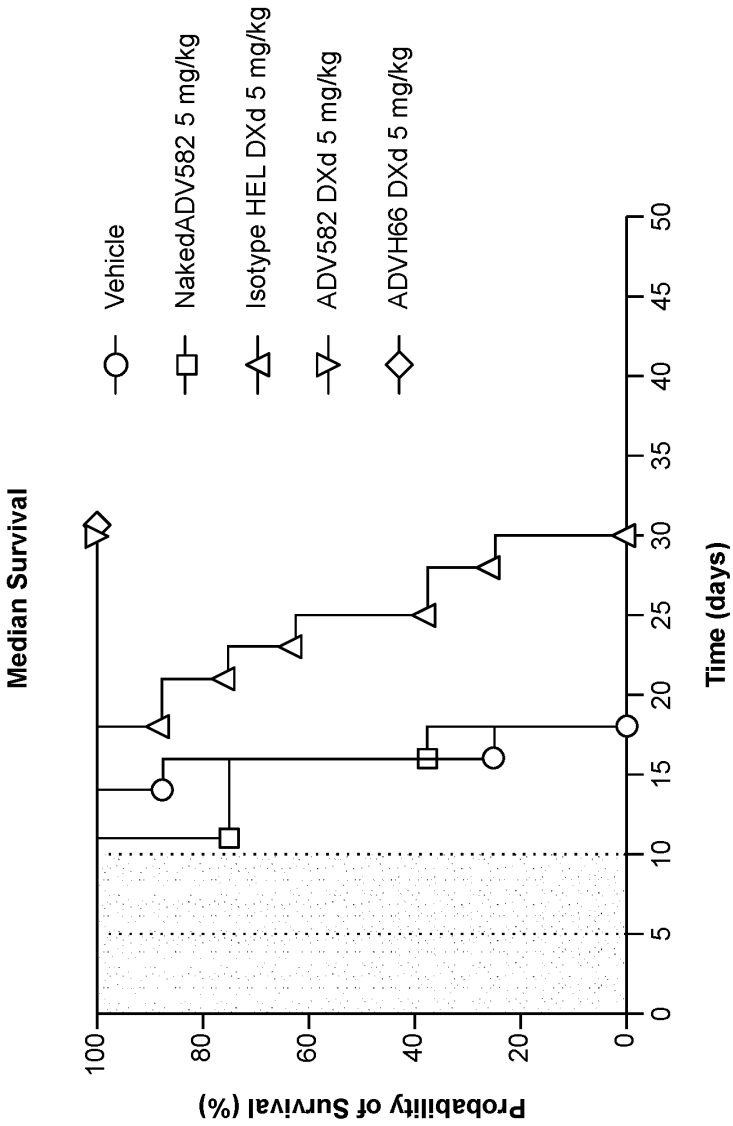

Median Survival
Vehicle
NakedADV582 5 mg/kg
Isotype HEL DXd 5 mg/kg
ADV582 DXd 5 mg/kg
ADVH66 DXd 5 mg/kg
Probability of Survival (%)
100
80
60
40
20
0
0
5
10
15
20
25
30
35
40
45
50
Time (days)

FIG. 32C

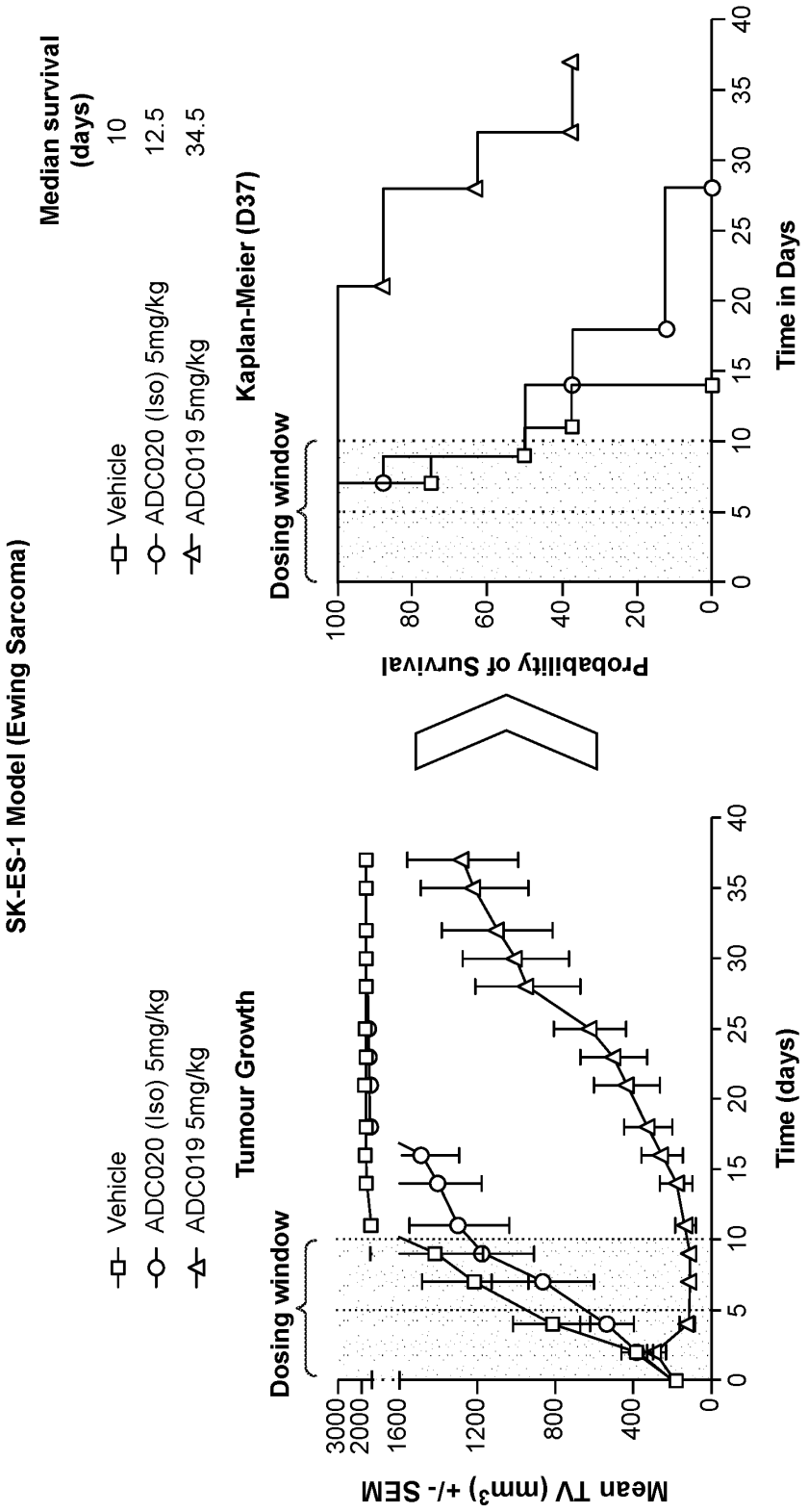

SK-ES-1 Model (Ewing Sarcoma)
Median survival (days)
Vehicle 10
ADC020 (Iso) 5mg/kg 12.5
ADC019 5mg/kg 34.5
Tumour Growth
Dosing window
Mean TV (mm3) +/- SEM
Time (days)
Kaplan-Meier (D37)
Dosing window
Probability of Survival
Time in Days

FIG. 33A

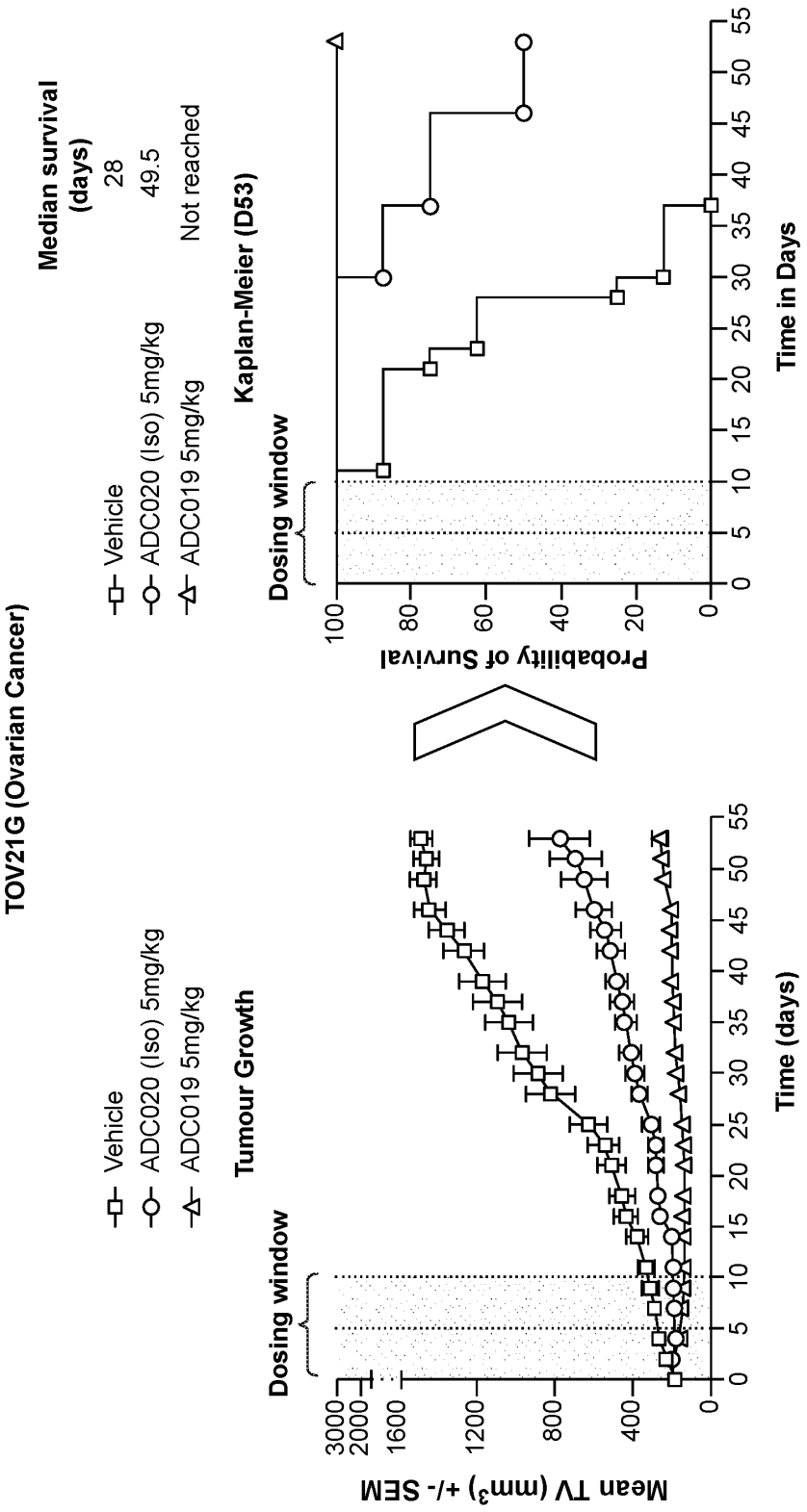

TOV21G (Ovarian Cancer)
Tumour Growth
Dosing window
Vehicle
ADC020 (Iso) 5mg/kg
ADC019 5mg/kg
Mean TV (mm3) +/- SEM
Time (days)
Kaplan-Meier (D53)
Probability of Survival
Time in Days
Median survival (days)
28
49.5
Not reached

FIG. 33B

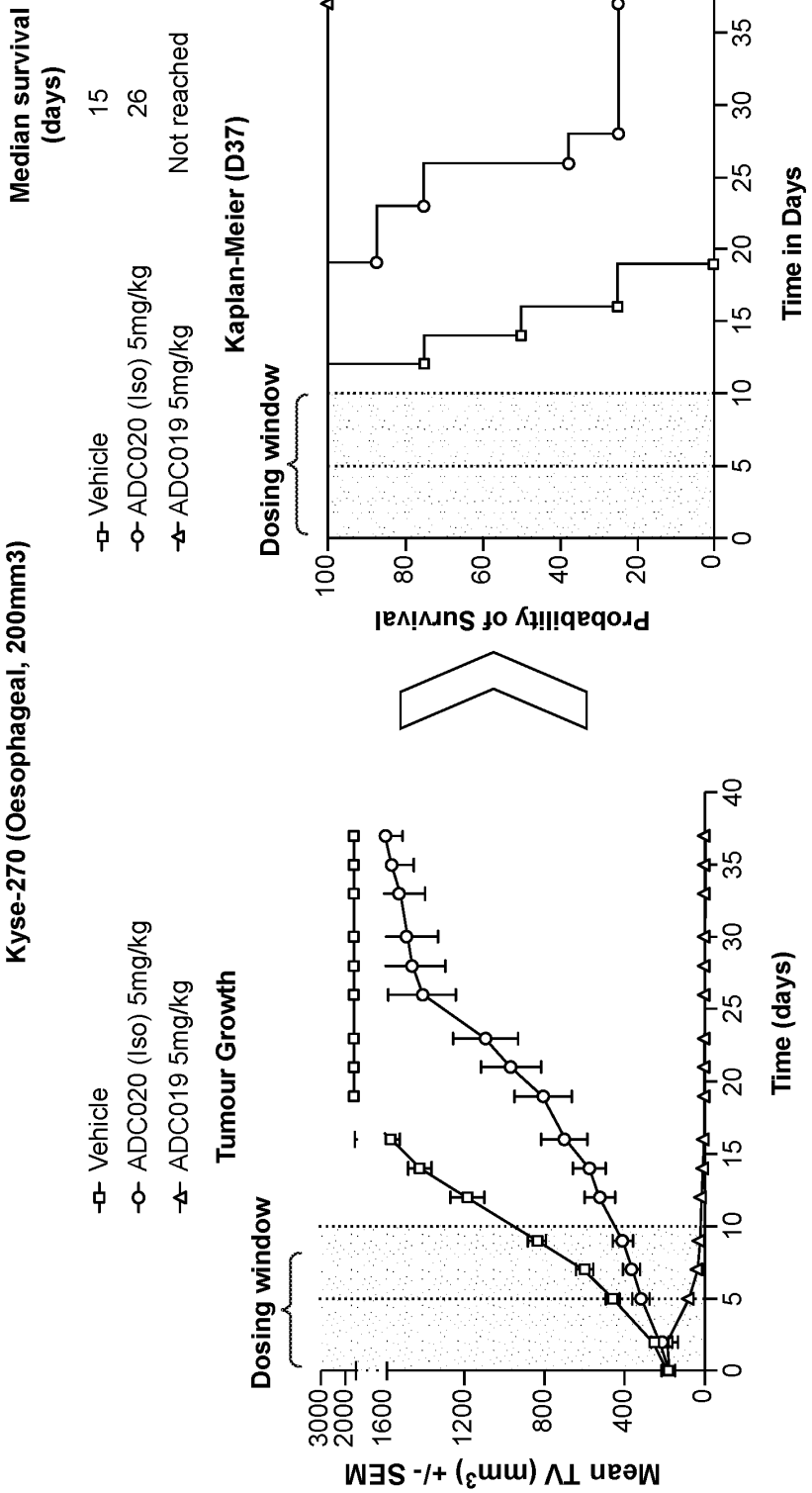

Kyse-270 (Oesophageal, 200mm3)
Tumour Growth
Dosing window
Vehicle
ADC020 (Iso) 5mg/kg
ADC019 5mg/kg
Mean TV (mm3) +/- SEM
Time (days)
Kaplan-Meier (D37)
Median survival (days)
15
26
Not reached
Probability of Survival
Time in Days

FIG. 33C

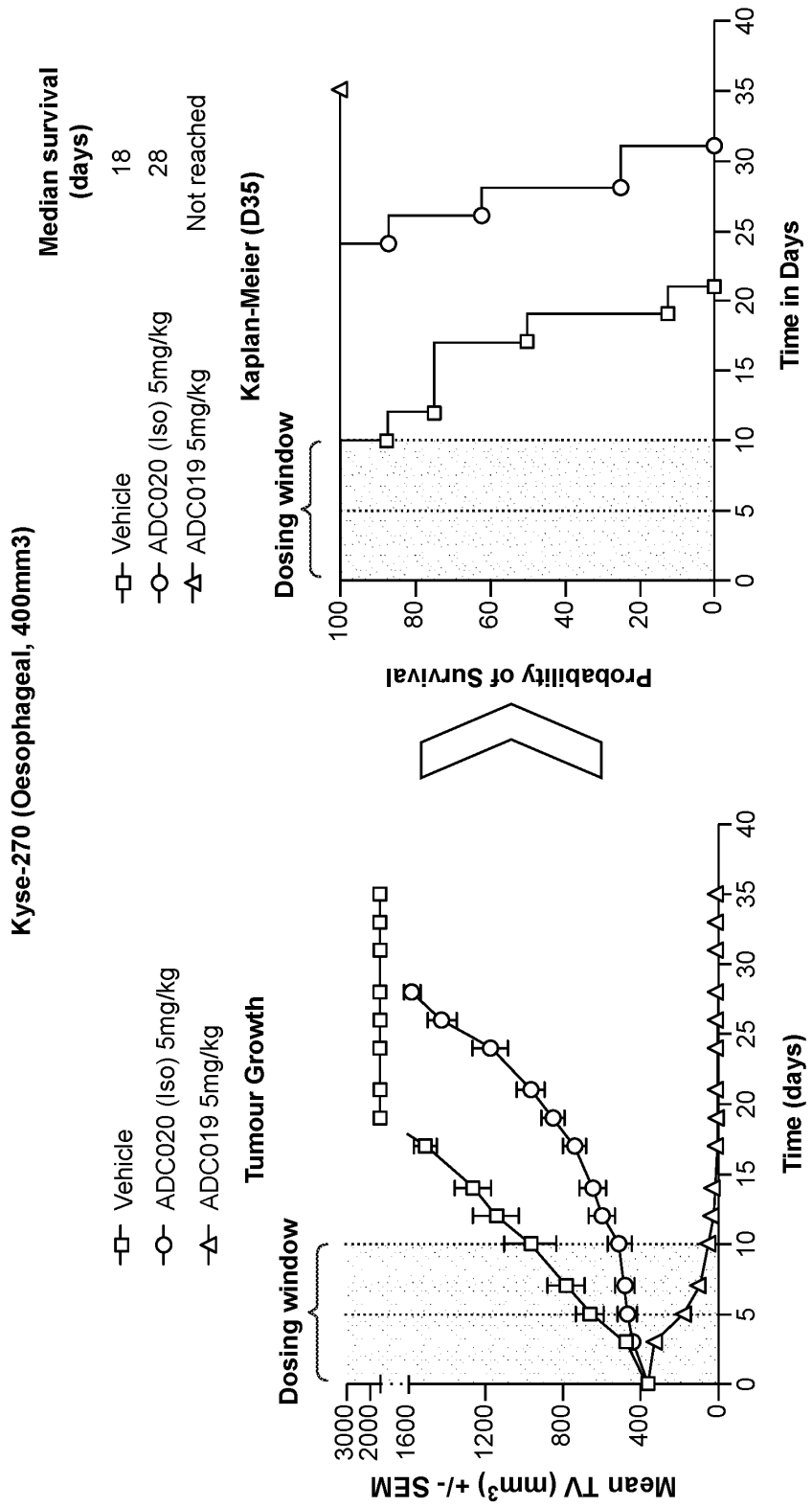

Kyse-270 (Oesophageal, 400mm3)
Tumour Growth
Dosing window
Vehicle
ADC020 (Iso) 5mg/kg
ADC019 5mg/kg
Mean TV (mm3) +/- SEM
Time (days)
Kaplan-Meier (D35)
Probability of Survival
Time in Days
Median survival (days)
18
28
Not reached

FIG. 33D

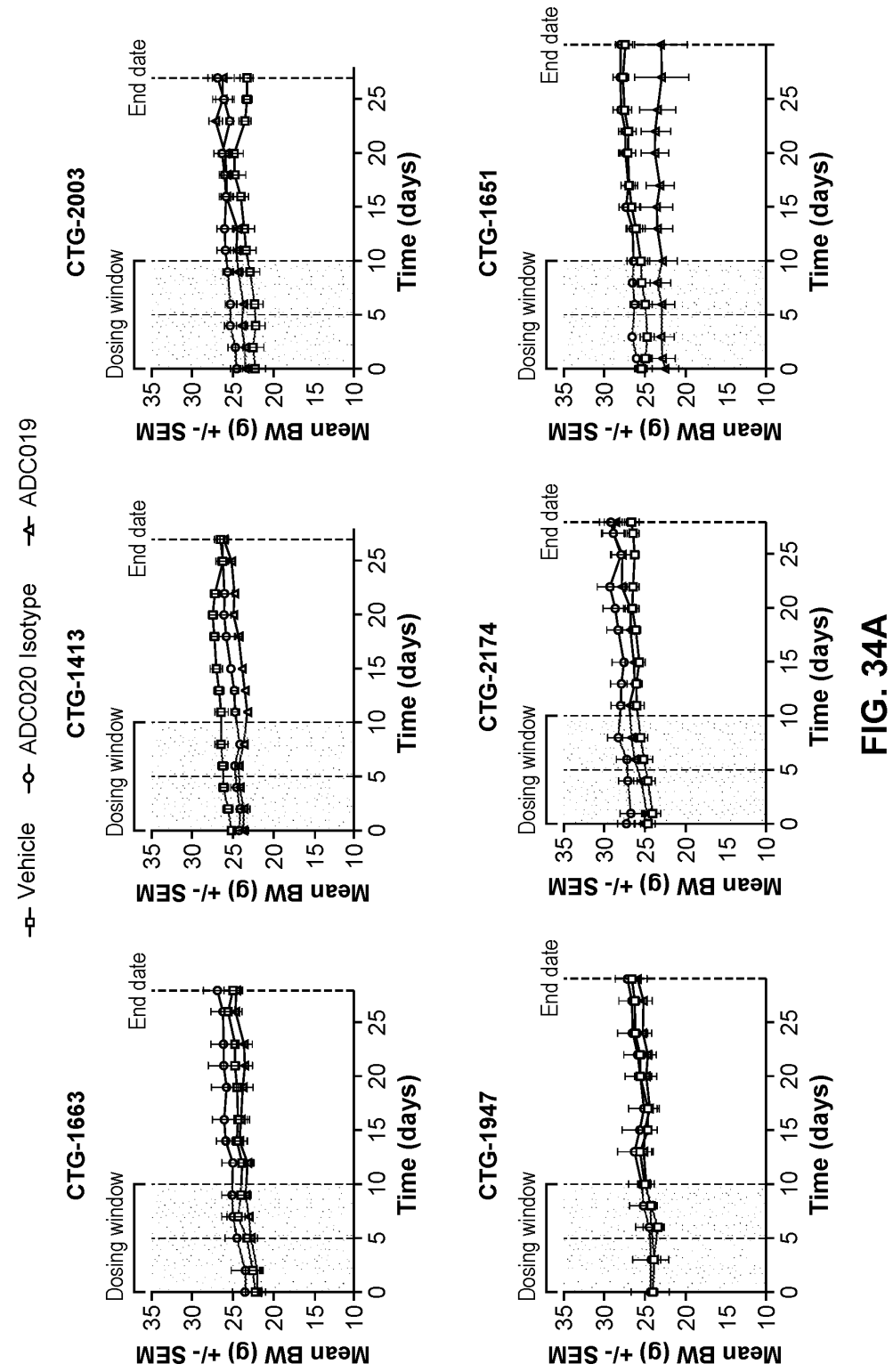

Vehicle
ADC020 Isotype
ADC019
CTG-2003
CTG-1651
CTG-1413
CTG-2174
CTG-1663
CTG-1947
Dosing window
End date
Mean BW (g) +/- SEM
Time (days)

FIG. 34A

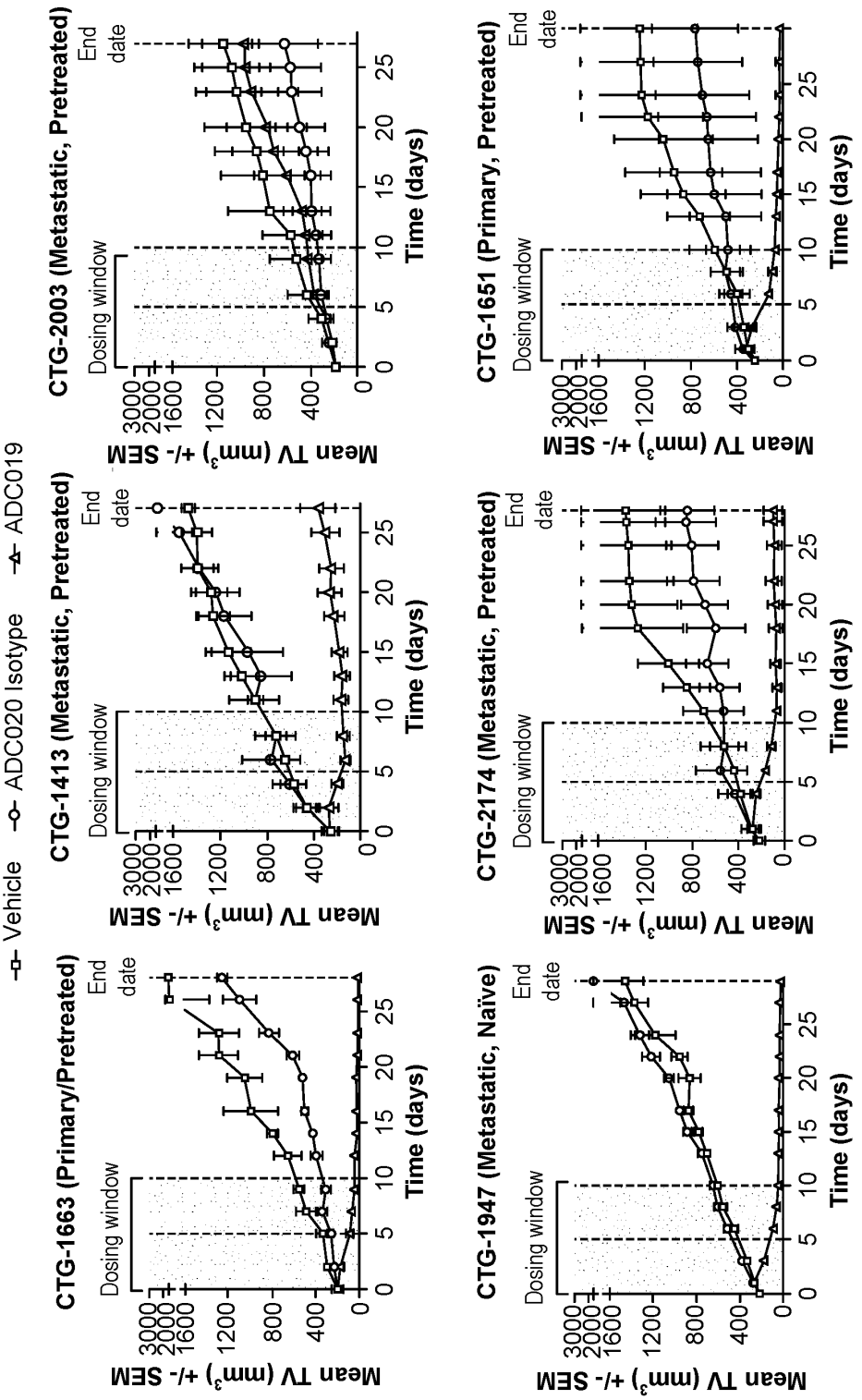
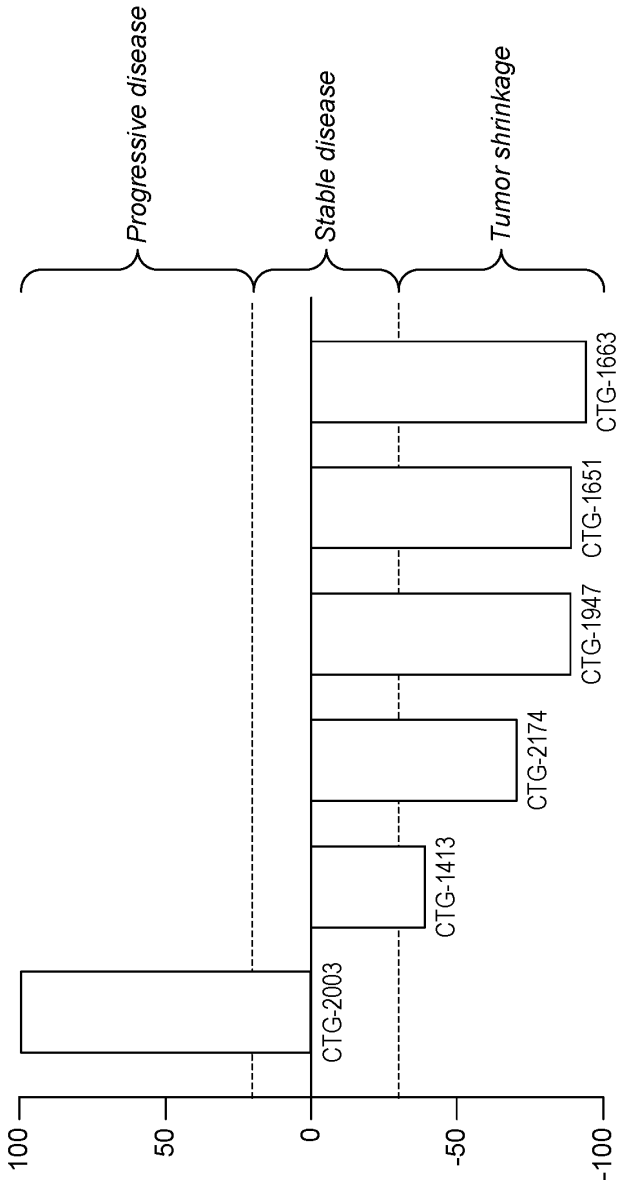

Vehicle
ADC020 Isotype
ADC019
CTG-1663 (Primary/Pretreated)
CTG-1413 (Metastatic, Pretreated)
CTG-2003 (Metastatic, Pretreated)
CTG-1947 (Metastatic, Naïve)
CTG-2174 (Metastatic, Pretreated)
CTG-1651 (Primary, Pretreated)
Dosing window
End date
Mean TV (mm³) +/- SEM
Time (days)

FIG. 34B



IL-1RAP RNA expression (Log2(TPM))	3.93	5.28	5.32	7.76	7.72	7.27
Tumor status	Metastatic	Metastatic	Metastatic	Primary	Metastatic	Primary
Topo isomerase inhibitor treatment history	Topo2-i pretreated **Topo1-i refractory**	Pretreated	Topo1/2-i pretreated	Topo1/2-i pretreated	Naive	Topo1-i pretreated **Topo1-i refractory**

FIG. 34C

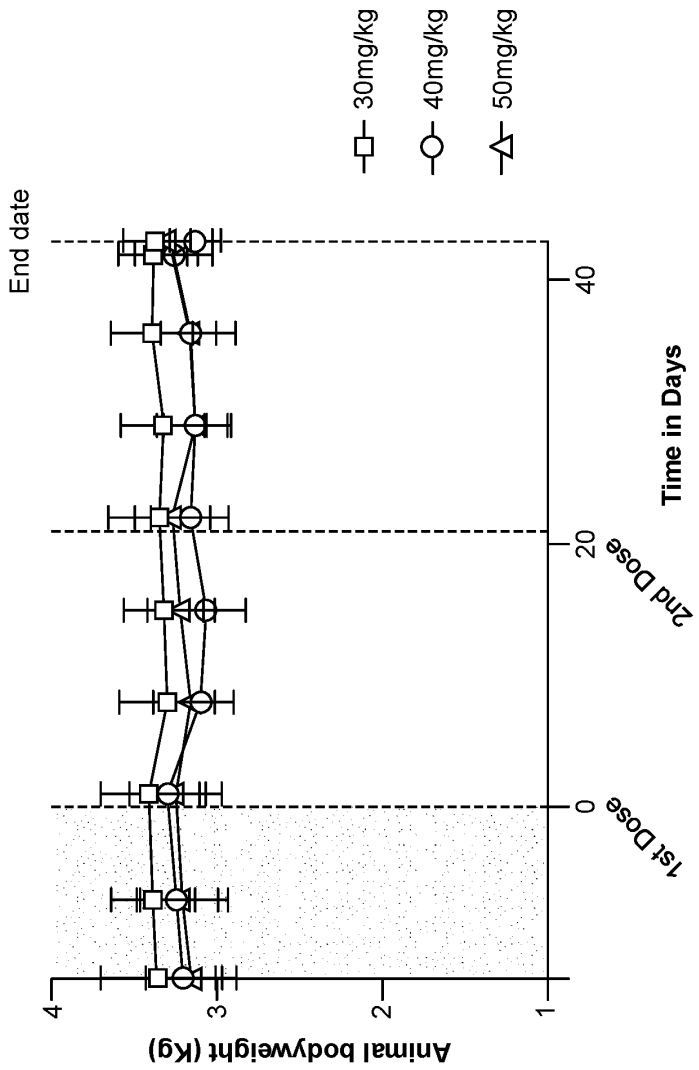

30mg/kg
40mg/kg
50mg/kg
End date
Animal bodyweight (Kg)
4
3
2
1
0
20
40
1st Dose
2nd Dose
Time in Days

FIG. 35

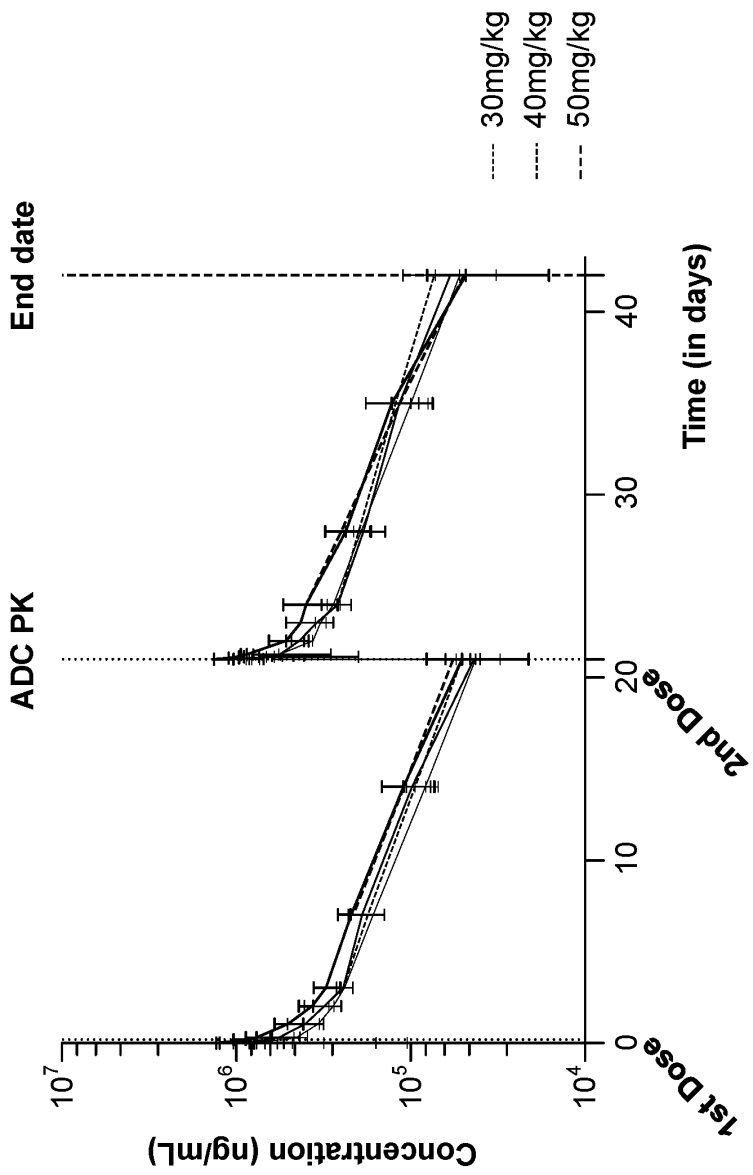

ADC PK
End date
30mg/kg
40mg/kg
50mg/kg
Concentration (ng/mL)
10^7
10^6
10^5
10^4
1st Dose
2nd Dose
0
10
20
30
40
Time (in days)

FIG. 36