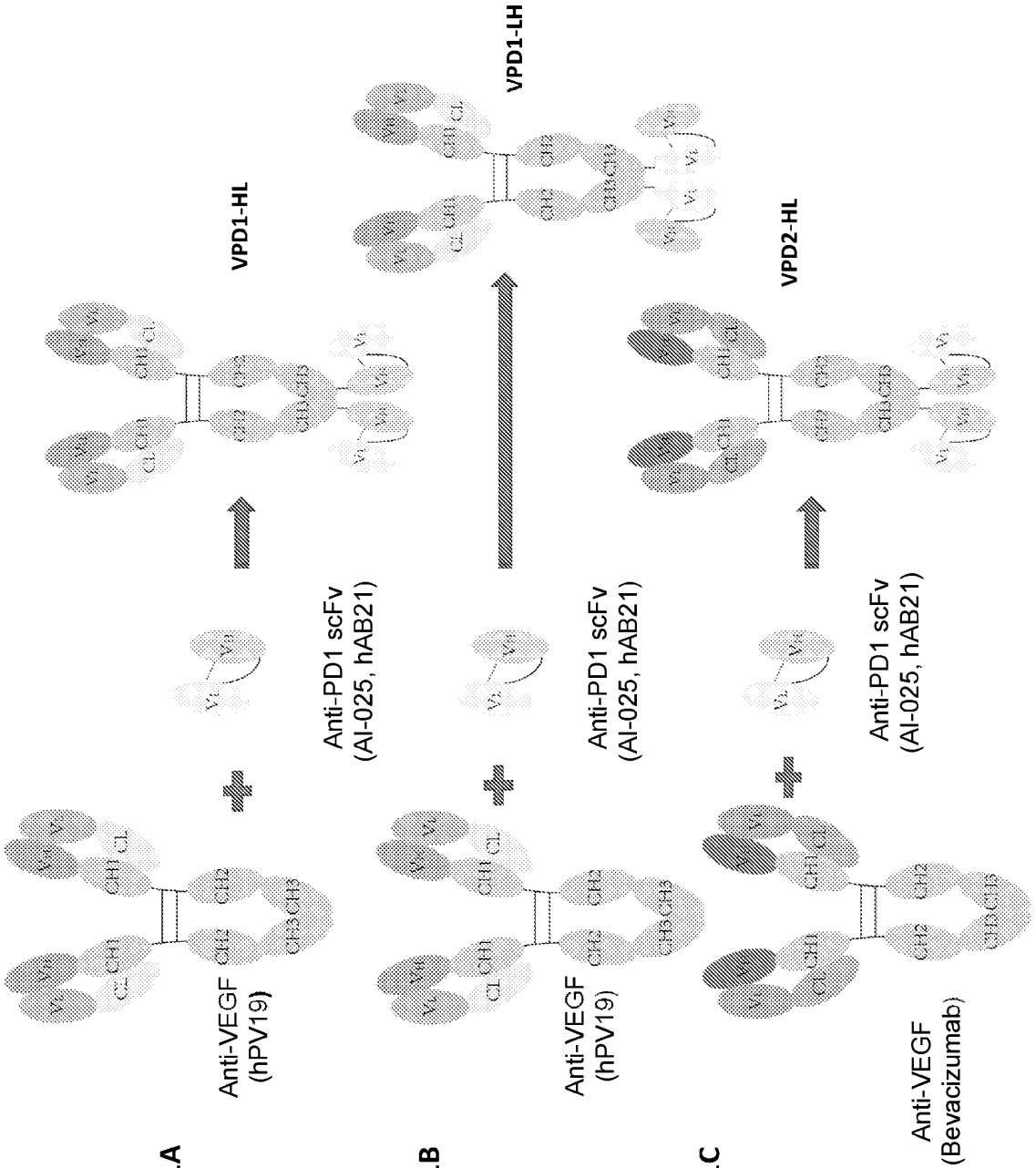


FIG. 1A

FIG. 1B

FIG. 1C

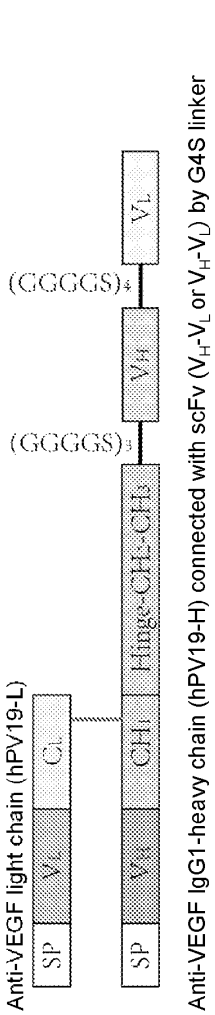

Anti-VEGF light chain (hPV19-L)
SP
V_L
C_L
Anti-VEGF IgG1-heavy chain (hPV19-H) connected with scFv (V_H-V_L or V_H-V_L) by G4S linker
SP
V_H
CH_1
Hinge-CH_2-CH_3
$(GGGGS)_3$
V_H
$(GGGGS)_4$
V_L

FIG. 2A

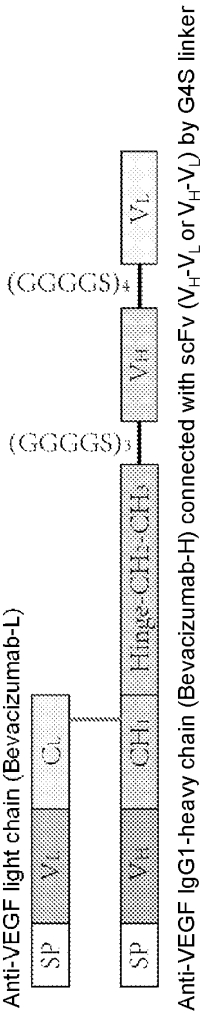

Anti-VEGF light chain (Bevacizumab-L)
SP
V_L
C_L
Anti-VEGF IgG1-heavy chain (Bevacizumab-H) connected with scFv (V_H-V_L or V_H-V_L) by G4S linker
SP
V_H
CH_1
Hinge-CH_2-CH_3
$(GGGGS)_3$
V_H
$(GGGGS)_4$
V_L

FIG. 2B

FIG. 3A

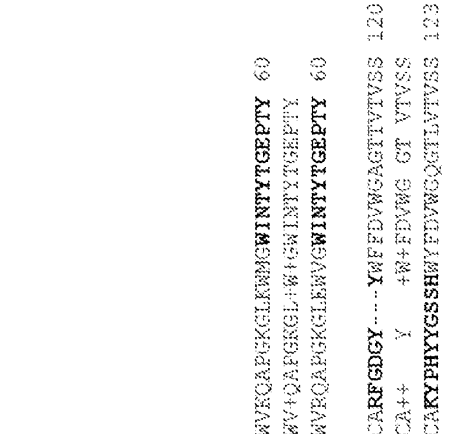

Identities: 81/133 (66%)
hPV19-VH
Bevacizumab
hPV19-VH
Bevacizumab
hPV19-VH
Bevacizumab

FIG. 3B

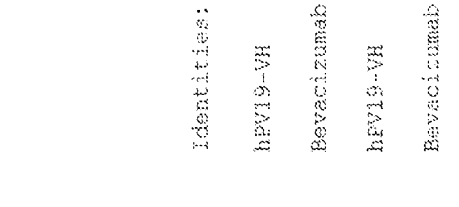

Identities: 69/113 (61%)
hPV19-VL
Bevacizumab
hPV19-VL
Bevacizumab

FIG. 4

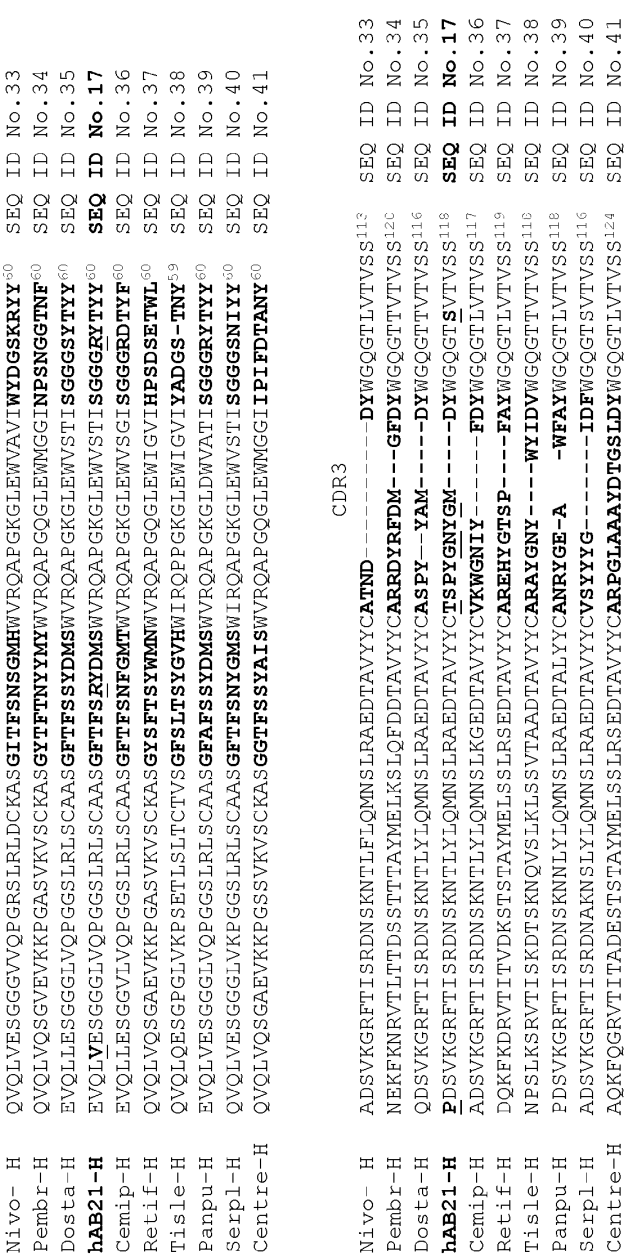

CDR1
CDR2
CDR3
Nivo- H
Pembr-H
Dosta-H
hAB21-H
Cemip-H
Retif-H
Tisle-H
Panpu-H
Serpl-H
Centre-H
SEQ ID No.33
SEQ ID No.34
SEQ ID No.35
SEQ ID No.17
SEQ ID No.36
SEQ ID No.37
SEQ ID No.38
SEQ ID No.39
SEQ ID No.40
SEQ ID No.41

FIG. 5

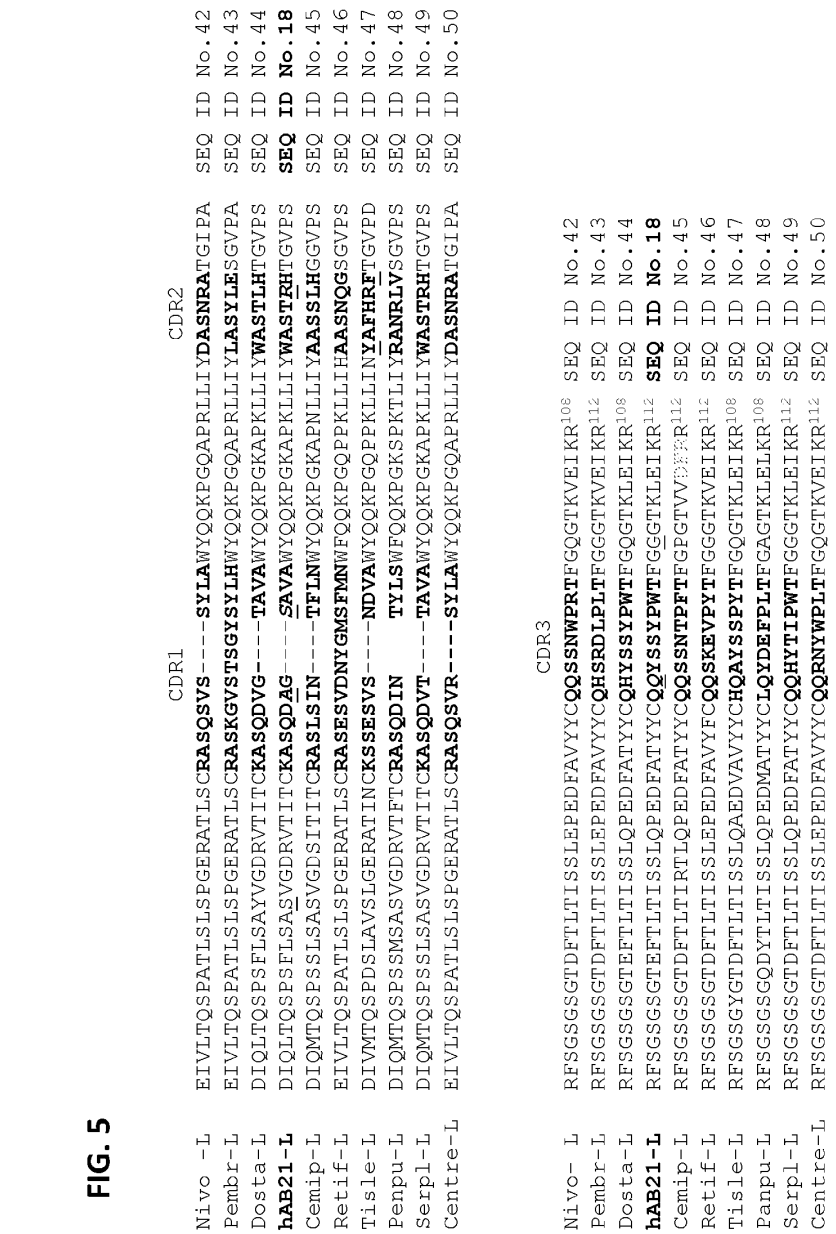

CDR1
CDR2
CDR3
Nivo -L EIVLTQSPATLSLSPGERATLSCRASQSVS----SYLAWYQQKPGQAPRLLIYDASNRATGIPA SEQ ID No.42
Pembr-L EIVLTQSPATLSLSPGERATLSCRASKGVSTSGYSYLHWYQQKPGQAPRLLIYLASYLESGVPA SEQ ID No.43
Dosta-L DIQLTQSPSFLSAYVGDRVTITCKASQDVG----TAVAWYQQKPGKAPKLLIYWASTLHTGVPS SEQ ID No.44
hAB21-L DIQLTQSPSFLSASVGDRVTITCKASQDAG----SAVAWYQQKPGKAPKLLIYWASTRHTGVPS SEQ ID No.18
Cemip-L DIQMTQSPSSLSASVGDSITITCRASLSIN----TFLNWYQQKPGKAPNLLIYAASSLHGGVPS SEQ ID No.45
Retif-L EIVLTQSPATLSLSPGERATLSCRASESVDNYGMSFMNWFQQKPGQPPKLLIHAASNQGSGVPS SEQ ID No.46
Tisle-L DIVMTQSPDSLAVSLGERATINCKSSESVS----NDVAWYQQKPGQPPKLLINYAFHRFTGVPD SEQ ID No.47
Penpu-L DIQMTQSPSSMSASVGDRVTFTCRASQDIN TYLSWFQQKPGKSPKTLIYRANRLVSGVPS SEQ ID No.48
Serpl-L DIQMTQSPSSLSASVGDRVTITCKASQDVT----TAVAWYQQKPGKAPKLLIYWASTRHTGVPS SEQ ID No.49
Centre-L EIVLTQSPATLSLSPGERATLSCRASQSVR----SYLAWYQQKPGQAPRLLIYDASNRATGIPA SEQ ID No.50
Nivo- L RFSGSGSGTDFTLTISSLEPEDFAVYYCQQSSNWPRTFGQGTKVEIKR106 SEQ ID No.42
Pembr-L RFSGSGSGTDFTLTISSLEPEDFAVYYCQHSRDLPLTFGGGTKVEIKR114 SEQ ID No.43
Dosta-L RFSGSGSGTEFTLTISSLQPEDFATYYCQHYSSYPWTFGQGTKLEIKR106 SEQ ID No.44
hAB21-L RFSGSGSGTEFTLTISSLQPEDFATYYCQQYSSYPWTFGGGTKLEIKR112 SEQ ID No.18
Cemip-L RFSGSGSGTDFTLTIRTLQPEDFATYYCQQSSNTPFTFGPGTVVXXXR112 SEQ ID No.45
Retif-L RFSGSGSGTDFTLTISSLEPEDFAVYFCQQSKEVPYTFGGGTKVEIKR112 SEQ ID No.46
Tisle-L RFSGSGYGTDFTLTISSLQAEDVAVYYCHQAYSSPYTFGQGTKLEIKR108 SEQ ID No.47
Panpu-L RFSGSGSGQDYTLTISSLQPEDMATYYCLQYDEFPLTFGAGTKLELKR108 SEQ ID No.48
Serpl-L RFSGSGSGTDFTLTISSLQPEDFATYYCQQHYTIPWTFGGGTKLEIKR112 SEQ ID No.49
Centre-L RFSGSGSGTDFTLTISSLEPEDFAVYYCQQRNYWPLTFGQGTKVEIKR112 SEQ ID No.50

FIG. 6A

```
Identities:  103/118(87%)
hAB21-VH     EVQLVESGGGLVQPGGSLRLSCAASGFTFSRYDMSWVRQAPGKGLEWVSTISGGGRYTYY60
             EVQLVESGGGLVQPGGSLRLSCAASGF FS YDMSWVRQAPGKGL+WV+TISGGGRYTYY
Penpulimab   EVQLVESGGGLVQPGGSLRLSCAASGFAFSSYDMSWVRQAPGKGLDWVATISGGGRYTYY60

hAB21-VH     PDSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCTSPYGNYGMDYWGQGTSVTVSS 118
             PDSVKGRFTISRDNSKN LYLQMNSLRAEDTA+YYC + YG     YWGQGT VTVSS
Penpulimab   PDSVKGRFTISRDNSKNNLYLQMNSLRAEDTALYYCANRYGEAWFAYWGQGTLVTVSS 118
```

FIG. 6B

```
Identities:  76/107(71%)
hAB21-VL     DIQLTQSPSFLSASVGDRVTITCKASQDAGSAVAWYQQKPGKAPKLLIYWASTRHTGVPS60
             DIQ+TQSPS +SASVGDRVT TC+ASQD  + ++W+QQKPGK+PK LIY A+   +GVPS
Penpulimab   DIQMTQSPSSMSASVGDRVTFTCRASQDINTYLSWFQQKPGKSPKTLIYRANRLVSGVPS60

hAB21-VL     RFSGSGSGTEFTLTISSLQPEDFATYYCQQYSSYPWTFGGGTKLEIK 107
             RFSGSGSG ++TLTISSLQPED ATYYC QY  +P TFG GTKLE+K
Penpulimab   RFSGSGSGQDYTLTISSLQPEDMATYYCLQYDEFPLTFGAGTKLELK 107
```

VPD1-HL: 99.33%

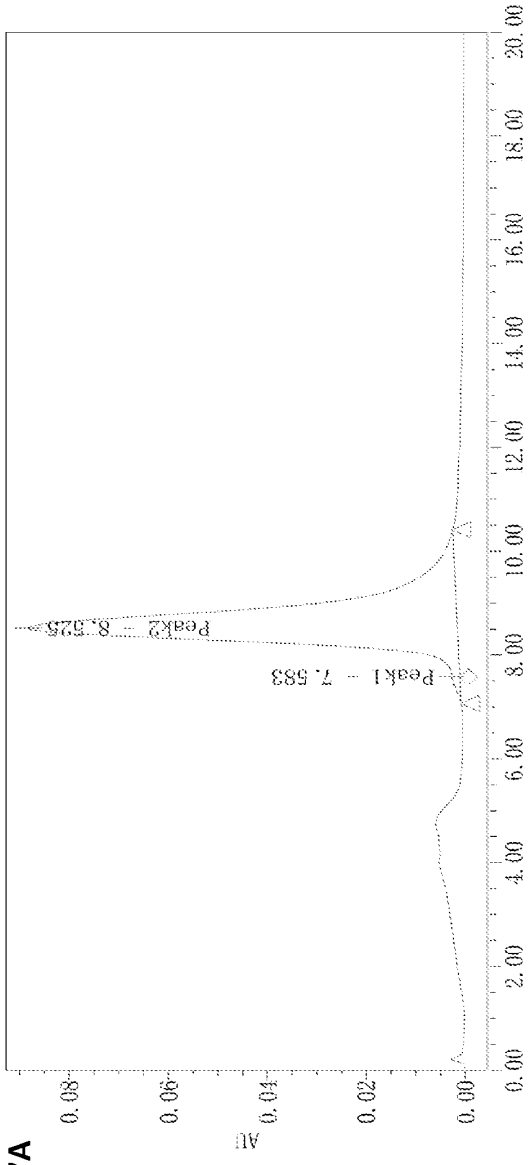


FIG. 7A

VPD1-LH: 92.29%

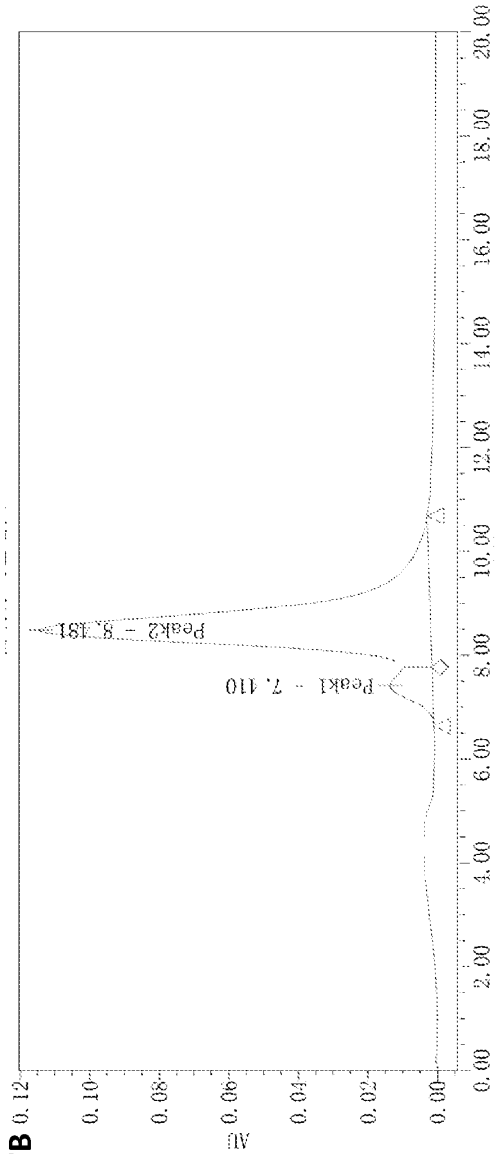


FIG. 7B

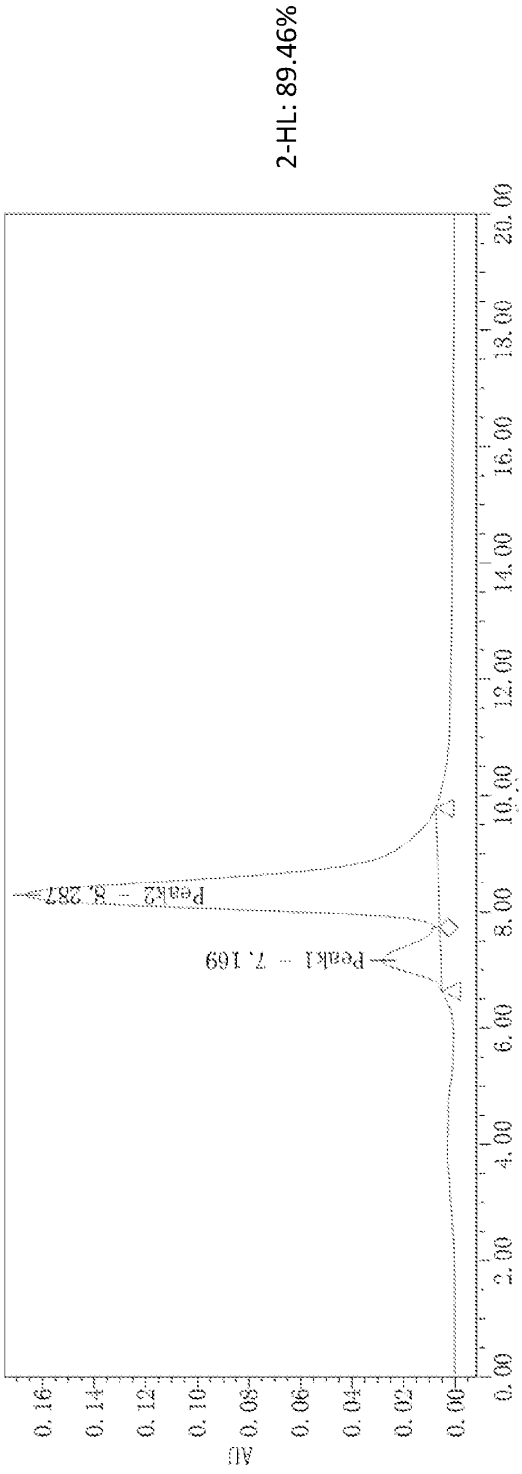

2-HL: 89.46%
AU
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0.00
0.00
2.00
4.00
6.00
8.00
10.00
12.00
14.00
16.00
18.00
20.00
Peak1 - 7.109
Peak2 - 8.287

FIG. 7C

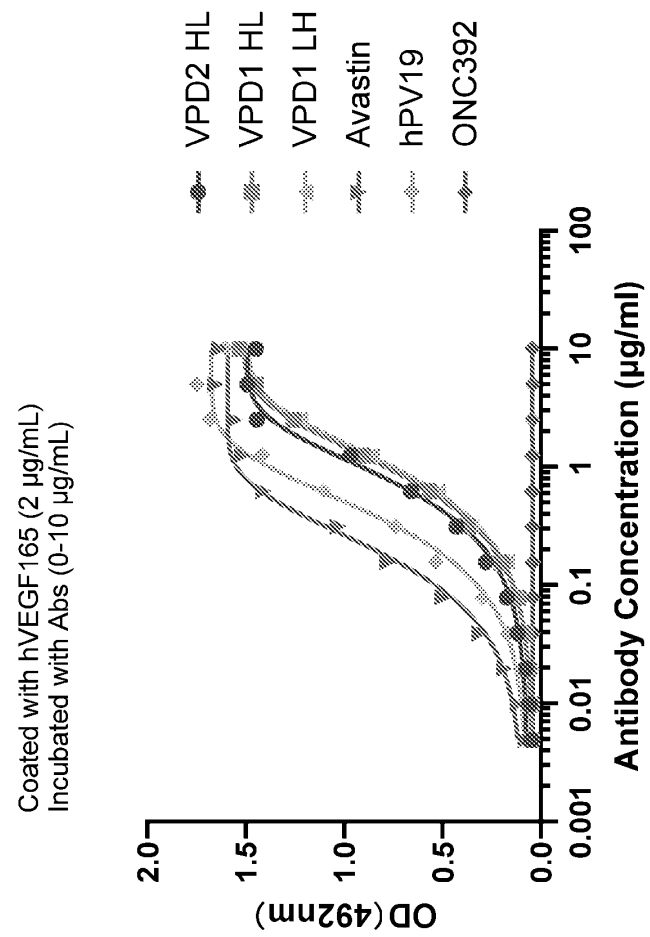

Coated with hVEGF165 (2 µg/mL)
Incubated with Abs (0-10 µg/mL)
VPD2 HL
VPD1 HL
VPD1 LH
Avastin
hPV19
ONC392
OD (492nm)
2.0
1.5
1.0
0.5
0.0
0.001
0.01
0.1
1
10
100
Antibody Concentration (µg/ml)

FIG. 8

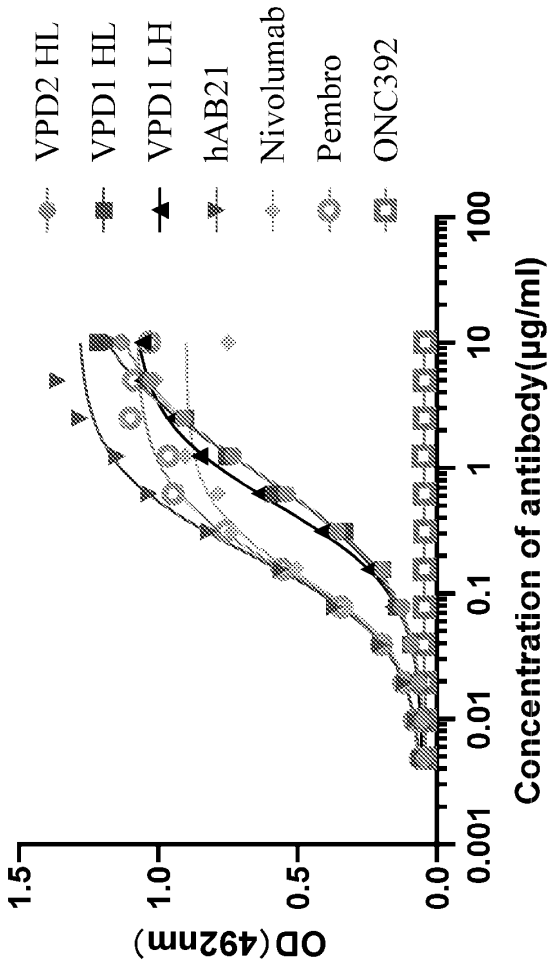

VPD2 HL
VPD1 HL
VPD1 LH
hAB21
Nivolumab
Pembro
ONC392
OD(492nm)
1.5
1.0
0.5
0.0
0.001
0.01
0.1
1
10
100
Concentration of antibody(μg/ml)

FIG. 9

FIG. 10A

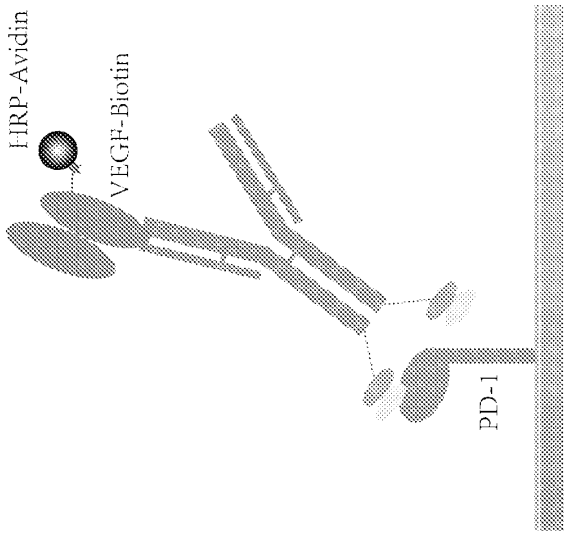


FIG. 10B

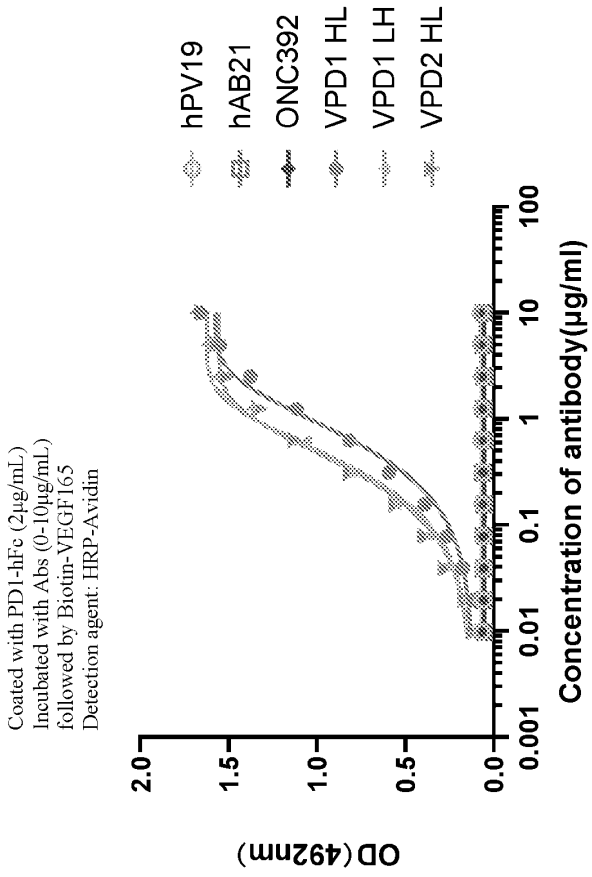


FIG. 11A

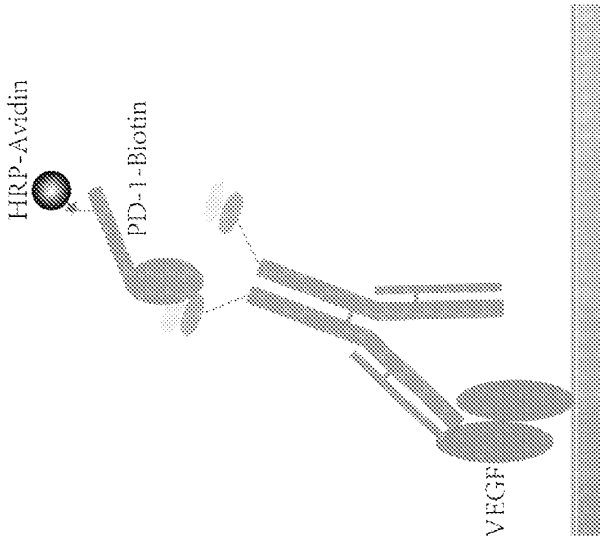
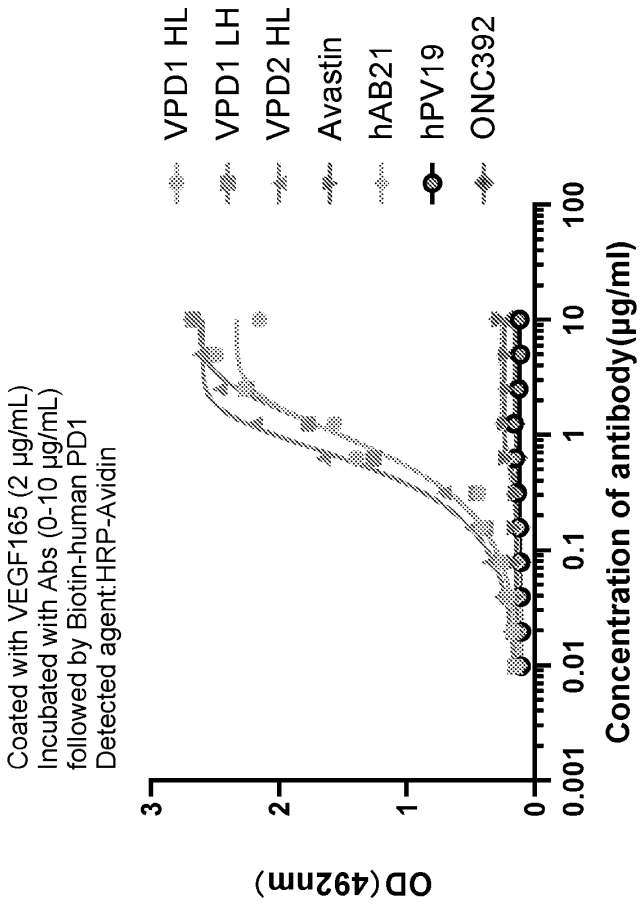


FIG. 11B



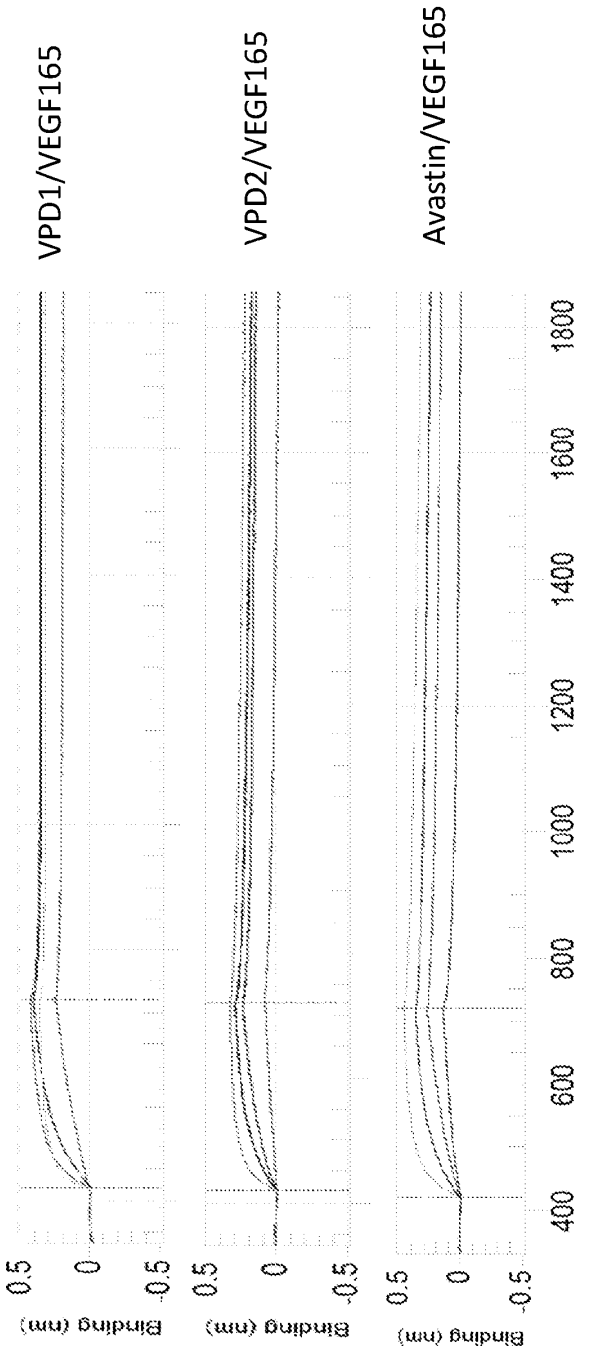

VPD1/VEGF165
VPD2/VEGF165
Avastin/VEGF165
Binding (nm)
0.5
0
-0.5
400
600
800
1000
1200
1400
1600
1800

FIG. 12

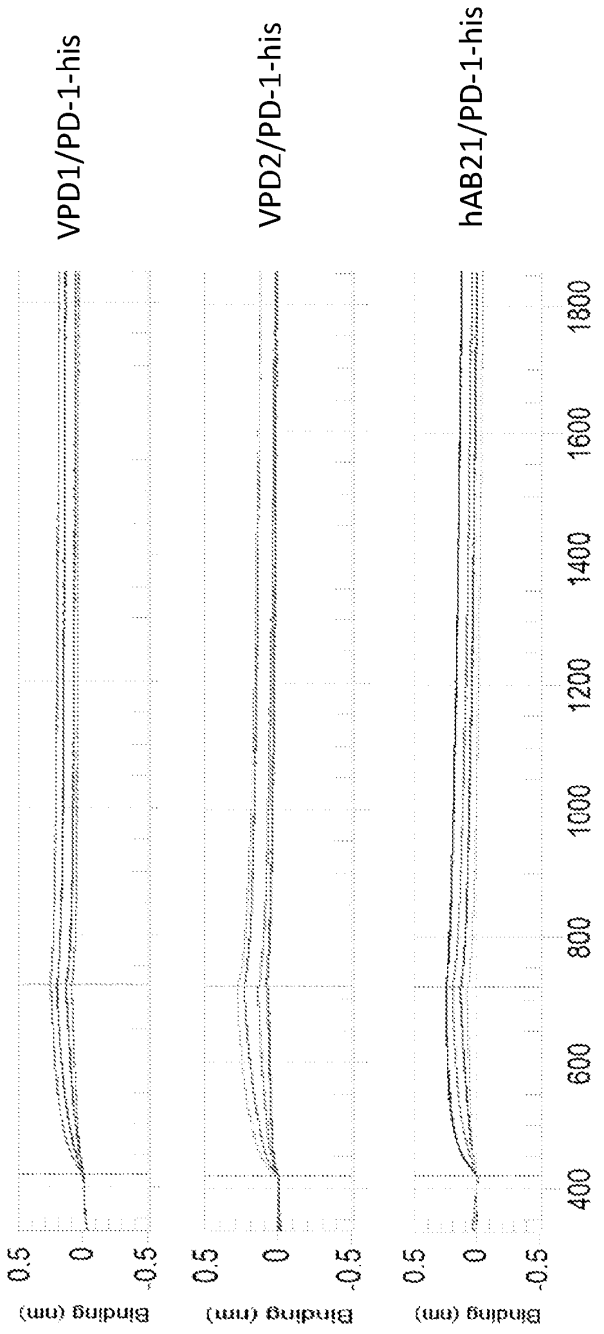

VPD1/PD-1-his
VPD2/PD-1-his
hAB21/PD-1-his
Binding (nm)
0.5
0
-0.5
400
600
800
1000
1200
1400
1600
1800

FIG. 13

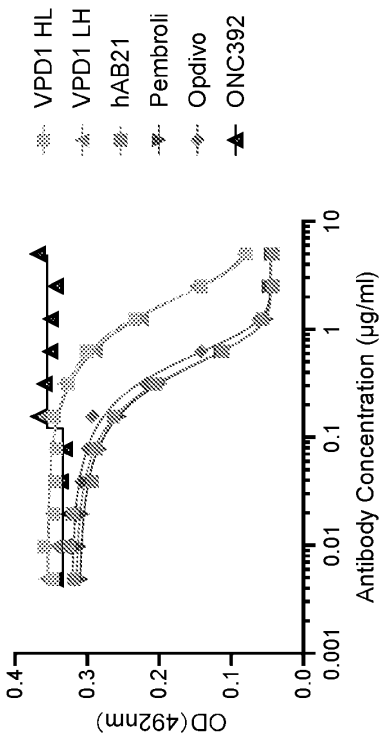

VPD1 HL
VPD1 LH
hAB21
Pembroli
Opdivo
ONC392
OD(492nm)
0.4
0.3
0.2
0.1
0.0
0.001
0.01
0.1
1
10
Antibody Concentration (µg/ml)

FIG. 14

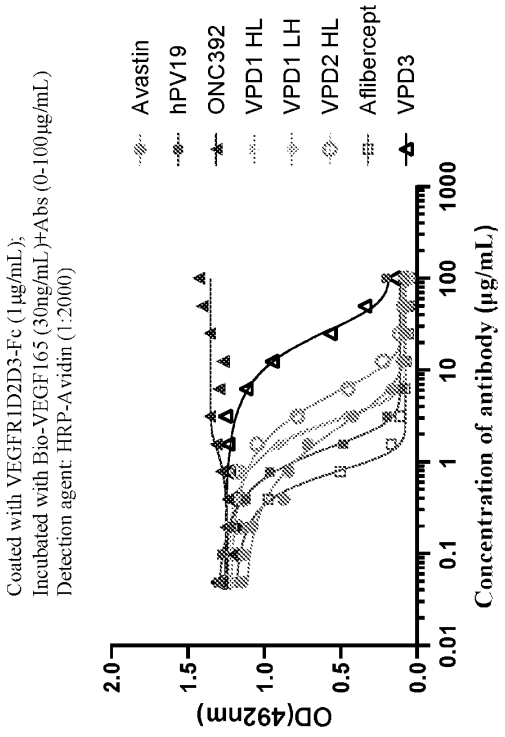

Coated with VEGFR1D2D3-Fc (1μg/mL);
Incubated with Bio-VEGF165 (30ng/mL)+Abs (0-100μg/mL)
Detection agent: HRP-Avidin (1:2000)
Avastin
hPV19
ONC392
VPD1 HL
VPD1 LH
VPD2 HL
Aflibercept
VPD3
OD(492nm)
2.0
1.5
1.0
0.5
0.0
0.01
0.1
1
10
100
1000
Concentration of antibody (μg/mL)

FIG. 15

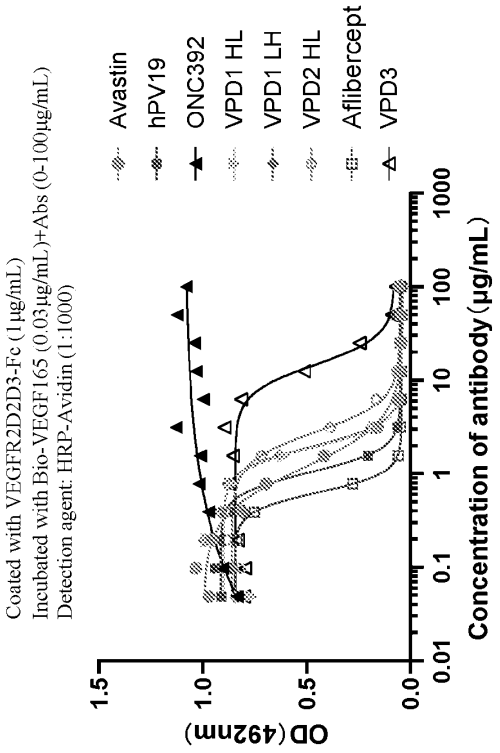

Coated with VEGFR2D2D3-Fc (1μg/mL)
Incubated with Bio-VEGF165 (0.03μg/mL)+Abs (0-100μg/mL)
Detection agent: HRP-Avidin (1:1000)
Avastin
hPV19
ONC392
VPD1 HL
VPD1 LH
VPD2 HL
Aflibercept
VPD3
OD (492nm)
1.5
1.0
0.5
0.0
0.01
0.1
1
10
100
1000
Concentration of antibody (μg/mL)

FIG. 16

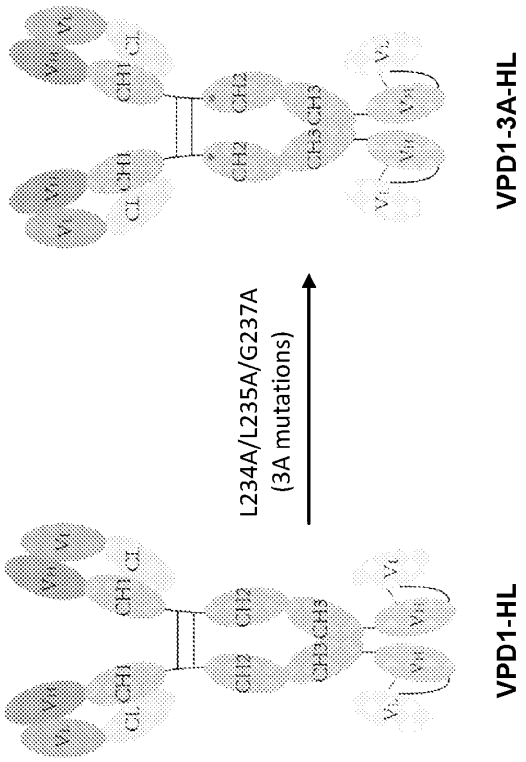


FIG. 17A

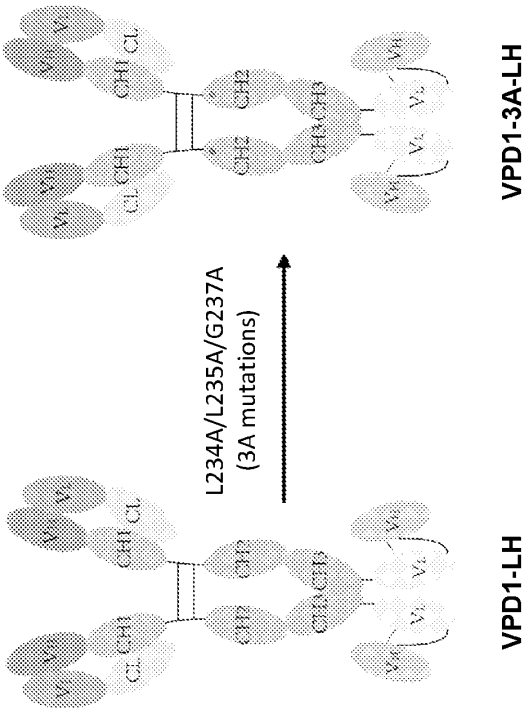


FIG. 17B

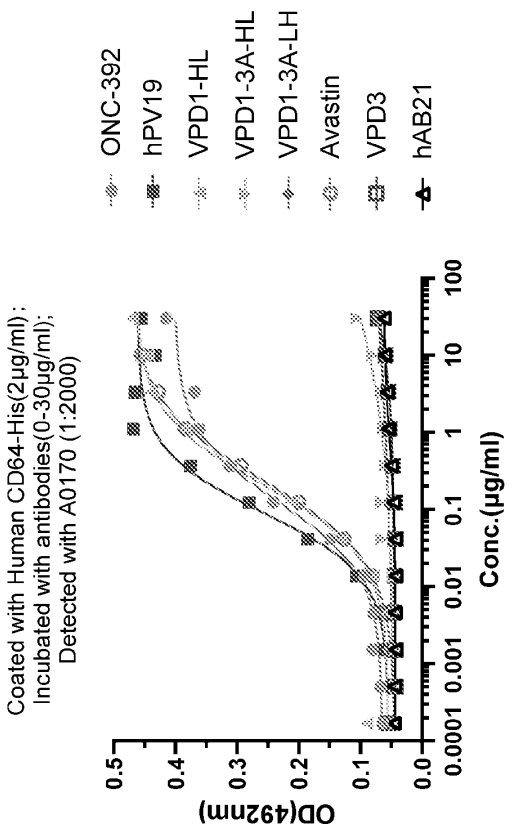

Coated with Human CD64-His(2μg/ml);
Incubated with antibodies(0-30μg/ml);
Detected with A0170 (1:2000)
OD(492nm)
0.0
0.1
0.2
0.3
0.4
0.5
0.0001
0.001
0.01
0.1
1
10
100
Conc.(μg/ml)
ONC-392
hPV19
VPD1-HL
VPD1-3A-HL
VPD1-3A-LH
Avastin
VPD3
hAB21

FIG. 18

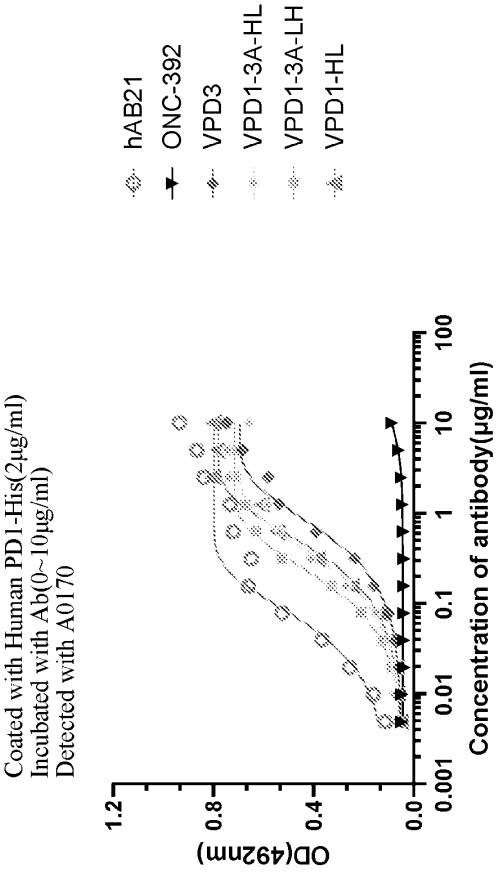

Coated with Human PD1-His(2μg/ml)
Incubated with Ab(0~10μg/ml)
Detected with A0170
hAB21
ONC-392
VPD3
VPD1-3A-HL
VPD1-3A-LH
VPD1-HL
OD(492nm)
1.2
0.8
0.4
0.0
0.001
0.01
0.1
1
10
100
Concentration of antibody(μg/ml)

FIG. 19

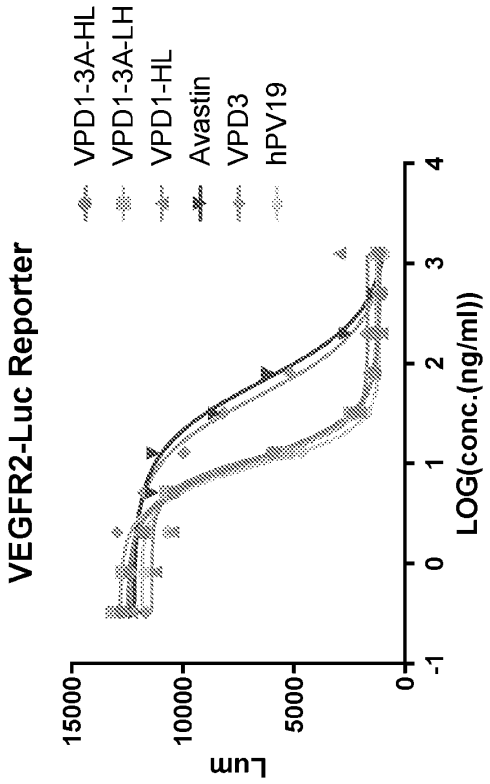

VEGFR2-Luc Reporter
VPD1-3A-HL
VPD1-3A-LH
VPD1-HL
Avastin
VPD3
hPV19
Lum
15000
10000
5000
0
-1
0
1
2
3
4
LOG(conc.(ng/ml))

FIG. 20

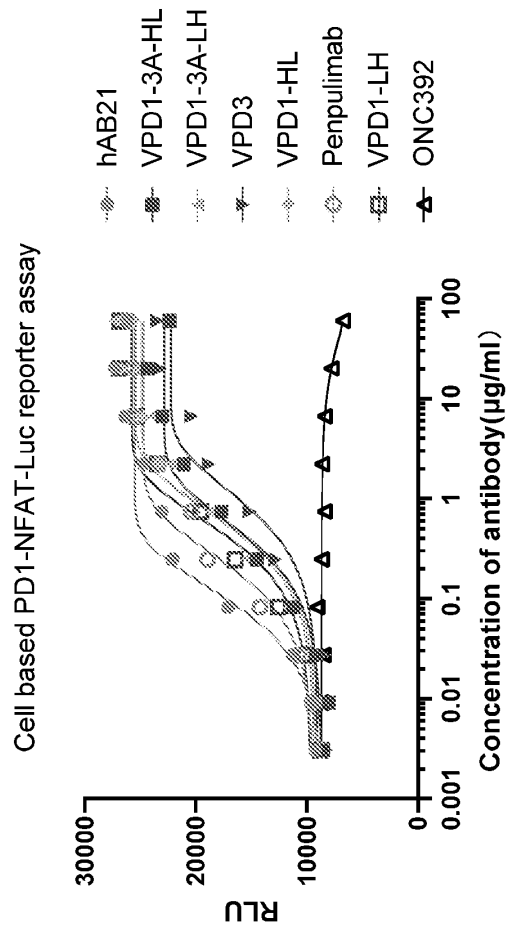

Cell based PD1-NFAT-Luc reporter assay
hAB21
VPD1-3A-HL
VPD1-3A-LH
VPD3
VPD1-HL
Penpulimab
VPD1-LH
ONC392
RLU
30000
20000
10000
0
0.001
0.01
0.1
1
10
100
Concentration of antibody(μg/ml)

FIG. 21

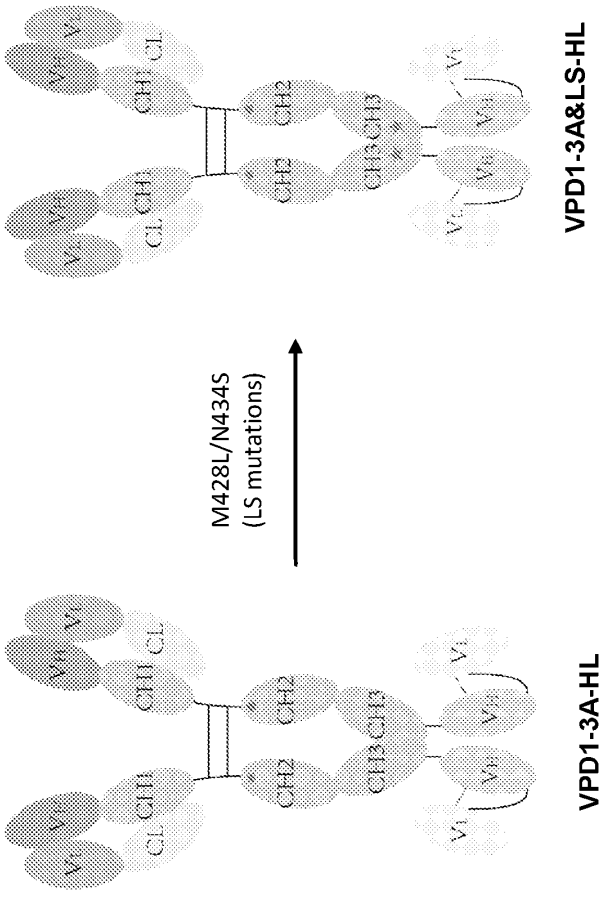


FIG. 22

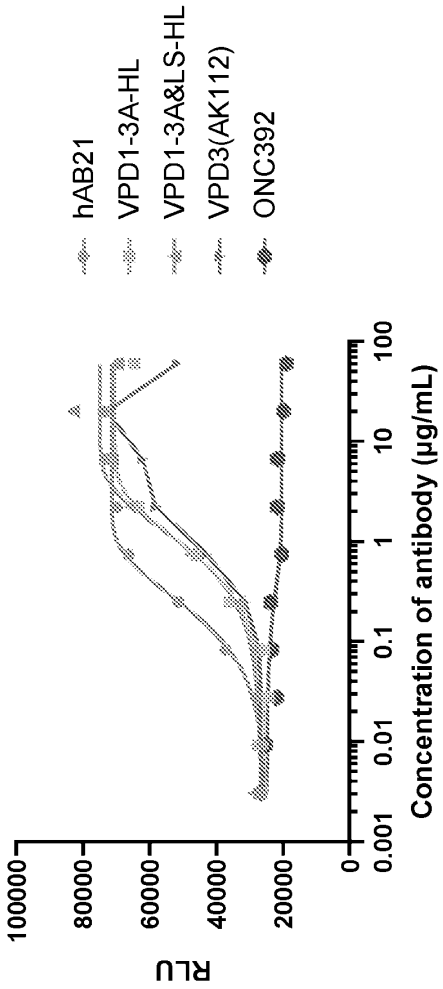

hAB21
VPD1-3A-HL
VPD1-3A&LS-HL
VPD3(AK112)
ONC392
RLU
100000
80000
60000
40000
20000
0
0.001
0.01
0.1
1
10
100
Concentration of antibody (μg/mL)

FIG. 23

FIG. 24

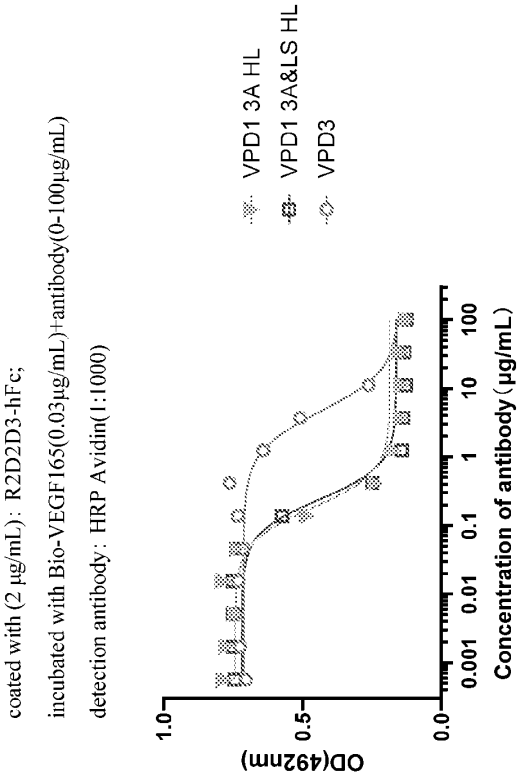

coated with (2 μg/mL): R2D2D3-hFc;
incubated with Bio-VEGF165(0.03μg/mL)+antibody(0-100μg/mL)
detection antibody: HRP Avidin(1:1000)
VPD1 3A HL
VPD1 3A&LS HL
VPD3
OD(492nm)
1.0
0.5
0.0
0.001
0.01
0.1
1
10
100
Concentration of antibody（μg/mL）

FIG. 25A

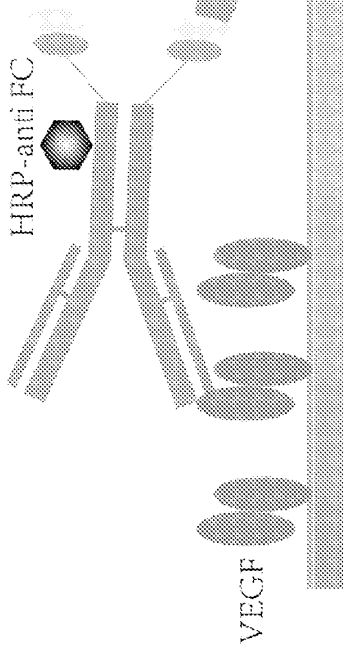


FIG. 25B

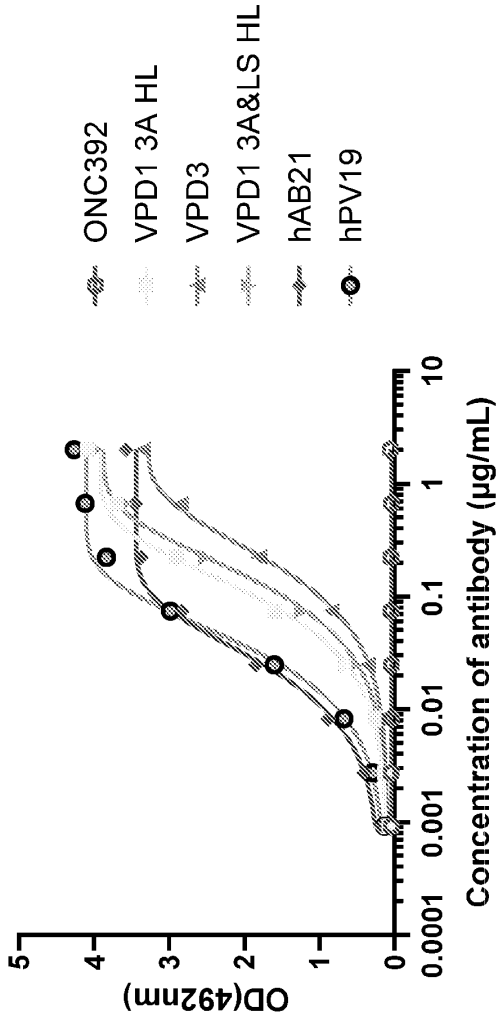


FIG. 26A

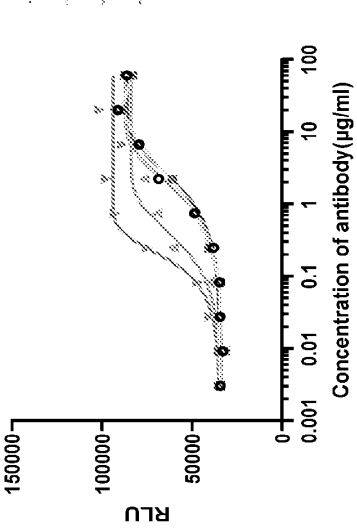


FIG. 26B

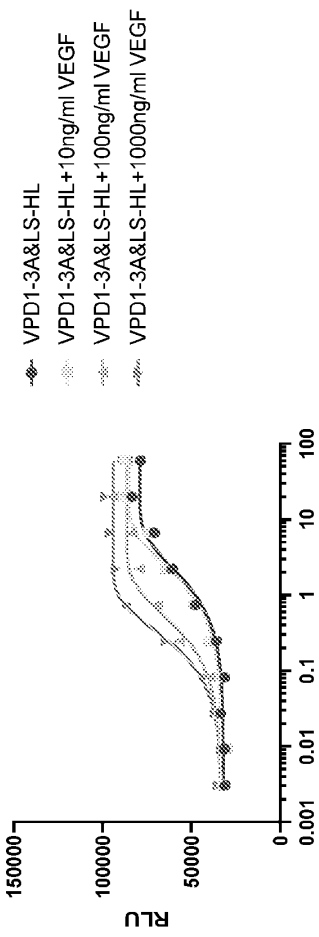
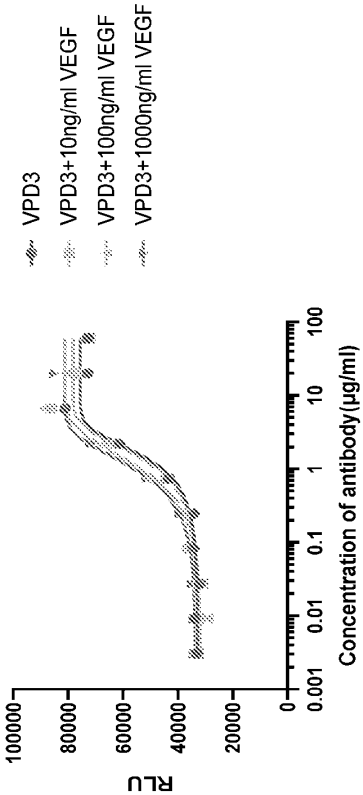


FIG. 26C



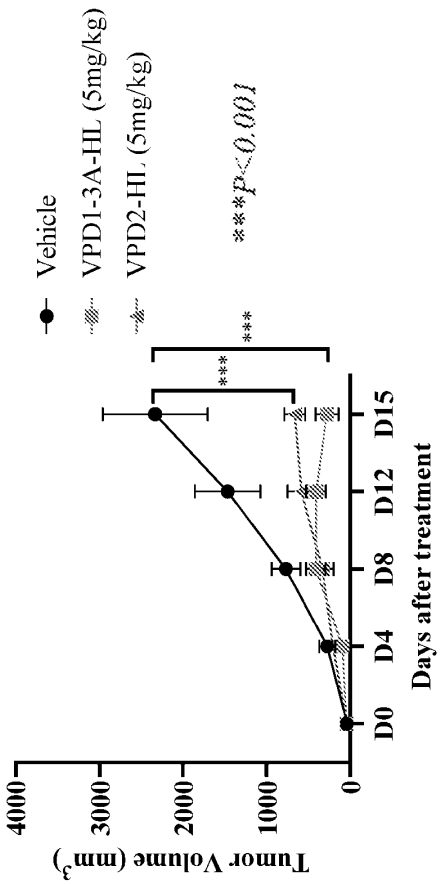

Vehicle
VPD1-3A-HL (5mg/kg)
VPD2-HL (5mg/kg)
***P<0.001
***
***
Tumor Volume (mm3)
4000
3000
2000
1000
0
D0
D4
D8
D12
D15
Days after treatment

FIG. 27

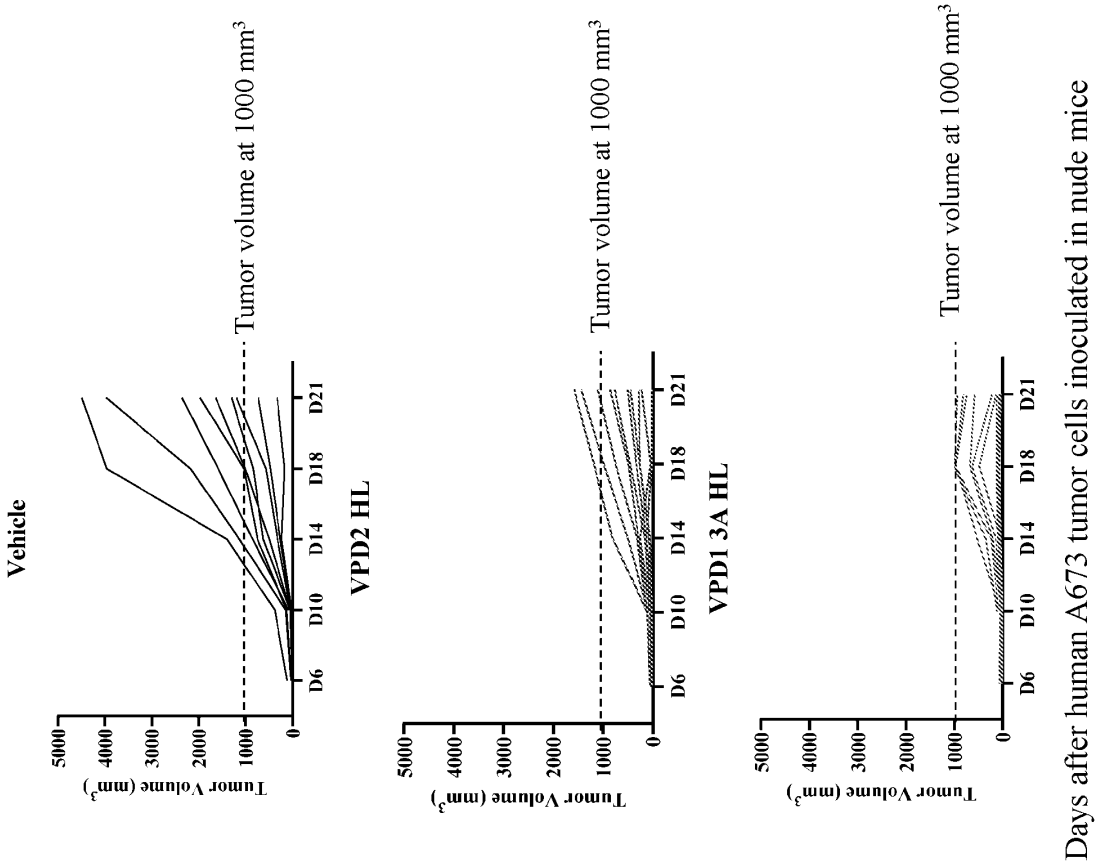

Vehicle
VPD2 HL
VPD1 3A HL
Tumor volume at 1000 mm3
Tumor Volume (mm3)
5000
4000
3000
2000
1000
0
D6
D10
D14
D18
D21
Days after human A673 tumor cells inoculated in nude mice

FIG. 28

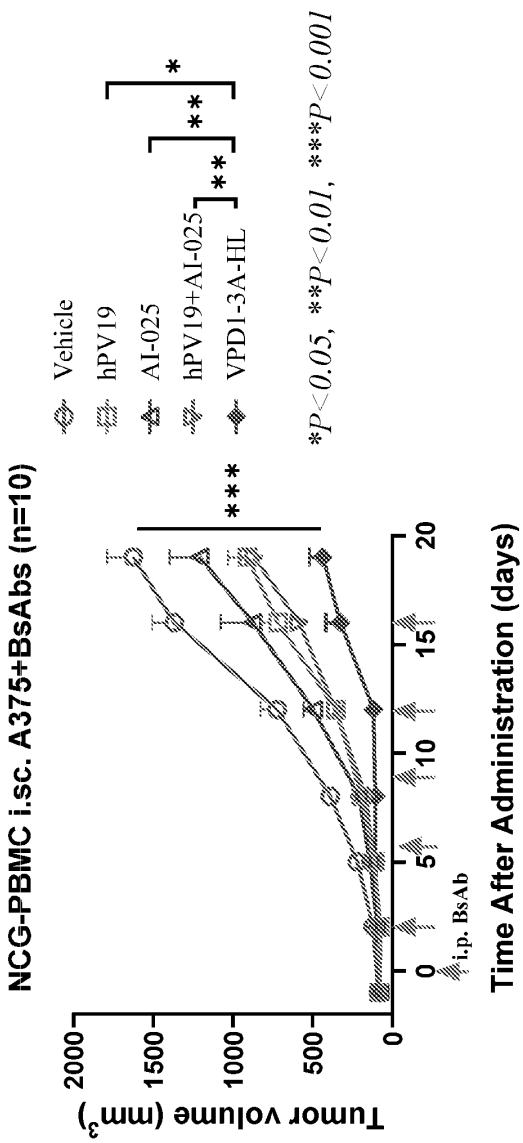

NCG-PBMC i.sc. A375+BsAbs (n=10)
Tumor volume (mm³)
2000
1500
1000
500
0
0
5
10
15
20
i.p. BsAb
Time After Administration (days)
***
*
**
**
Vehicle
hPV19
AI-025
hPV19+AI-025
VPD1-3A-HL
*P<0.05, **P<0.01, ***P<0.001

FIG. 29

FIG. 30B

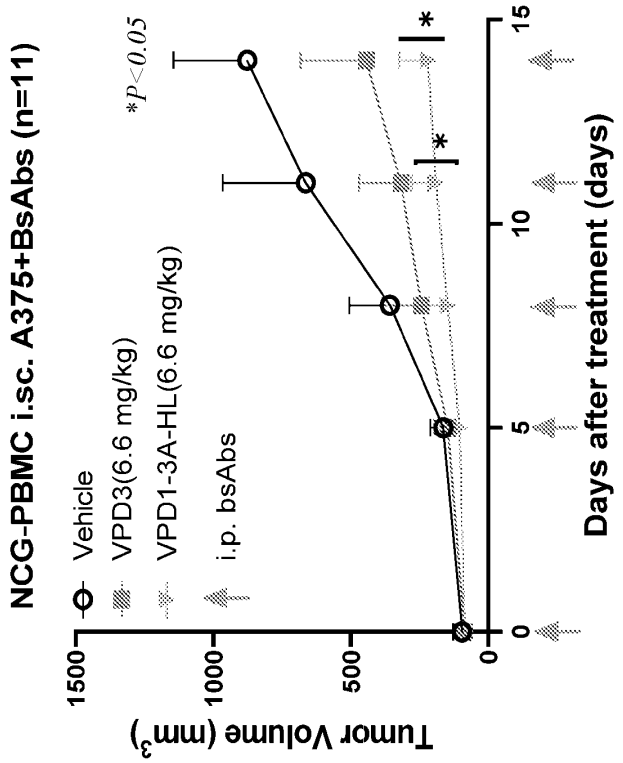
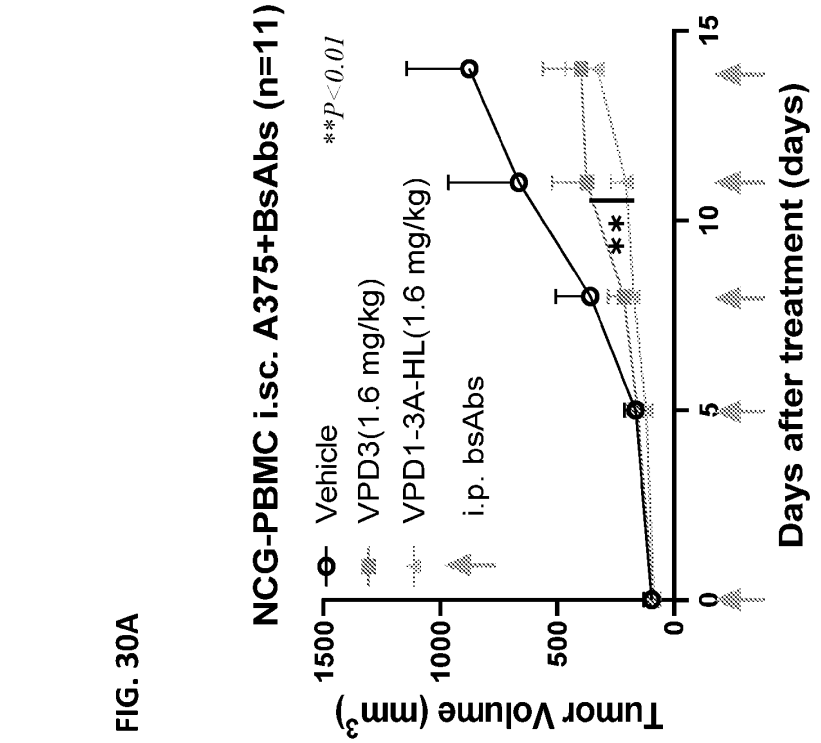


FIG. 30A



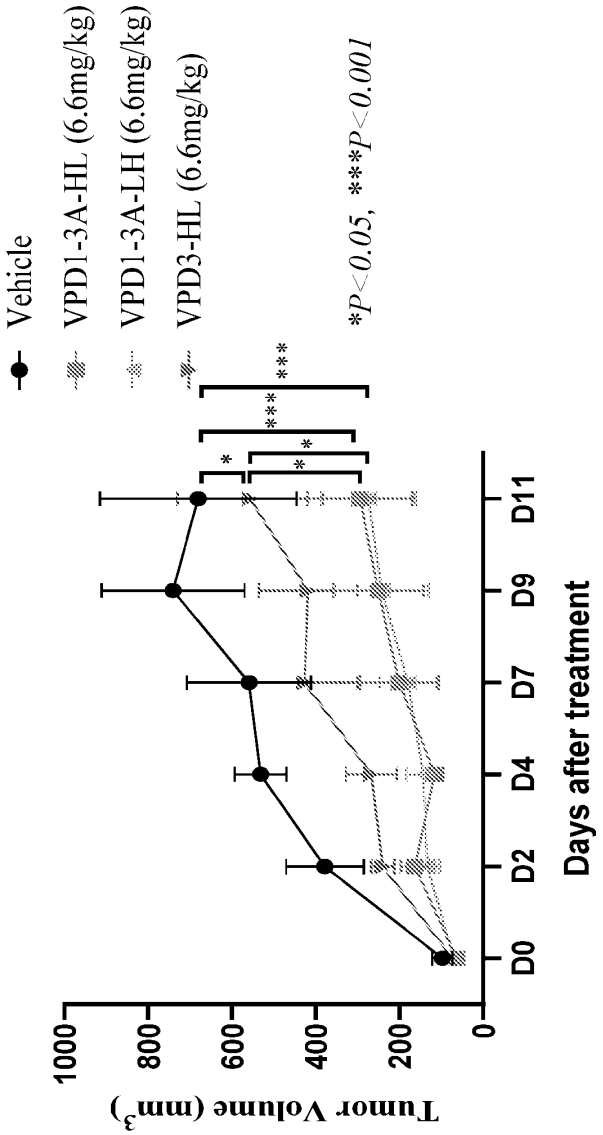

Vehicle
VPD1-3A-HL (6.6mg/kg)
VPD1-3A-LH (6.6mg/kg)
VPD3-HL (6.6mg/kg)
*P<0.05, ***P<0.001
Tumor Volume (mm3)
1000
800
600
400
200
0
D0
D2
D4
D7
D9
D11
Days after treatment
*
*
*
***
***

FIG. 31

FIG. 32

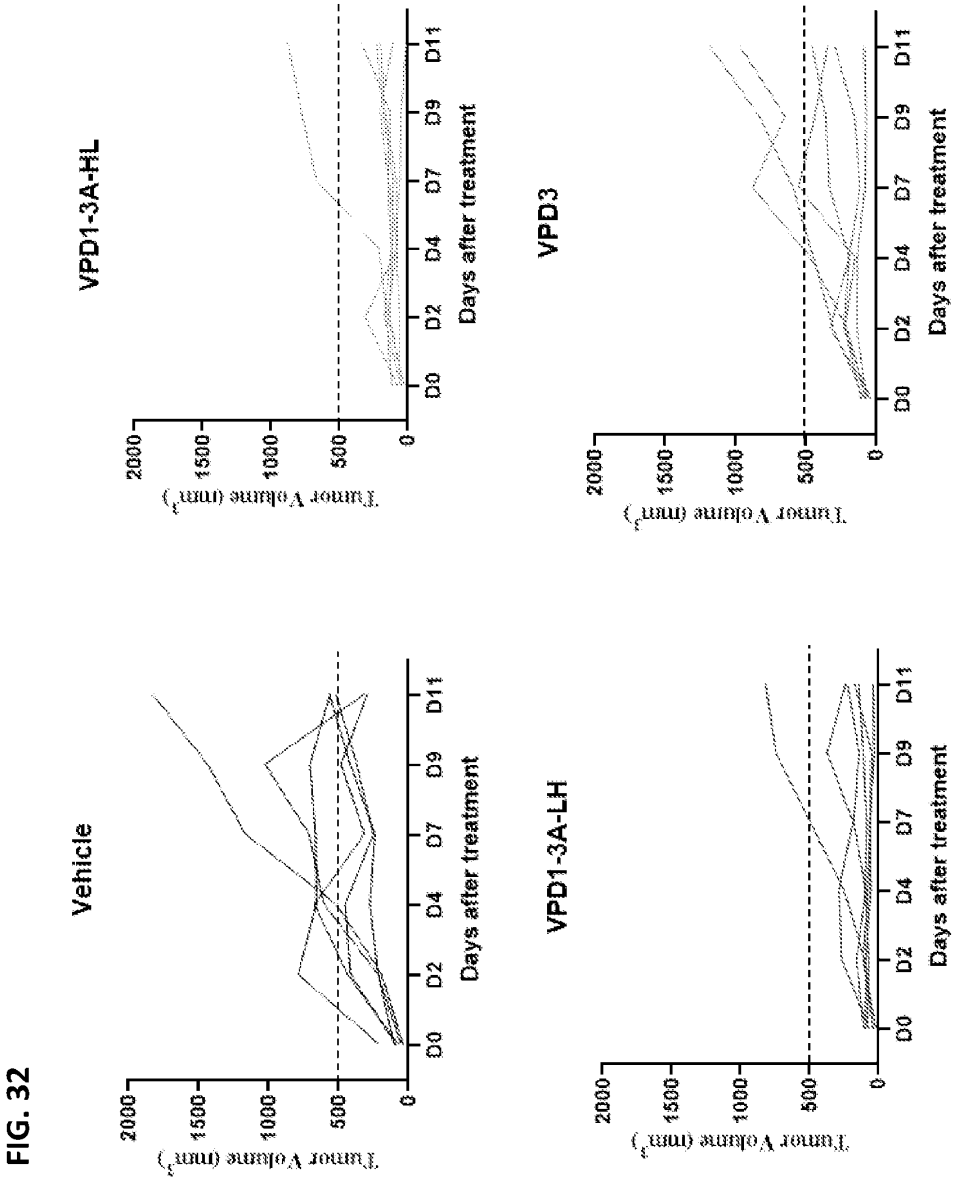

Vehicle
VPD1-3A-HL
VPD3
VPD1-3A-LH
Tumor Volume (mm³)
2000
1500
1000
500
0
D0
D2
D4
D7
D9
D11
Days after treatment

FIG. 33B

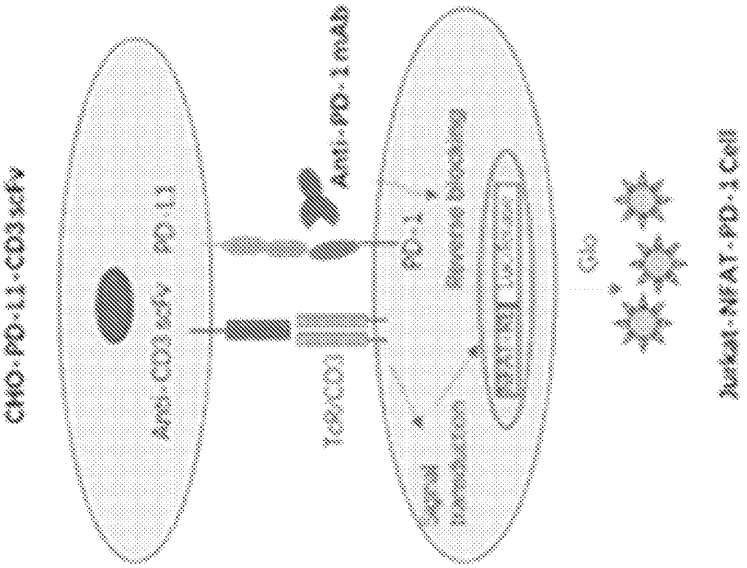


FIG. 33A

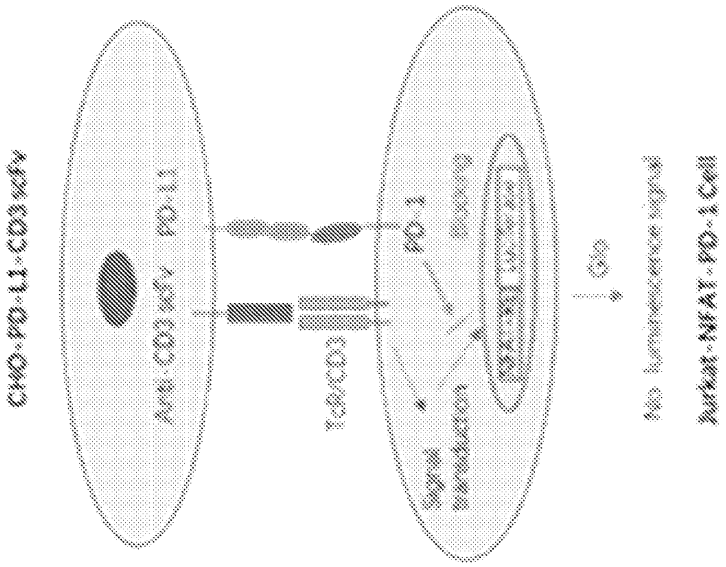


FIG. 34

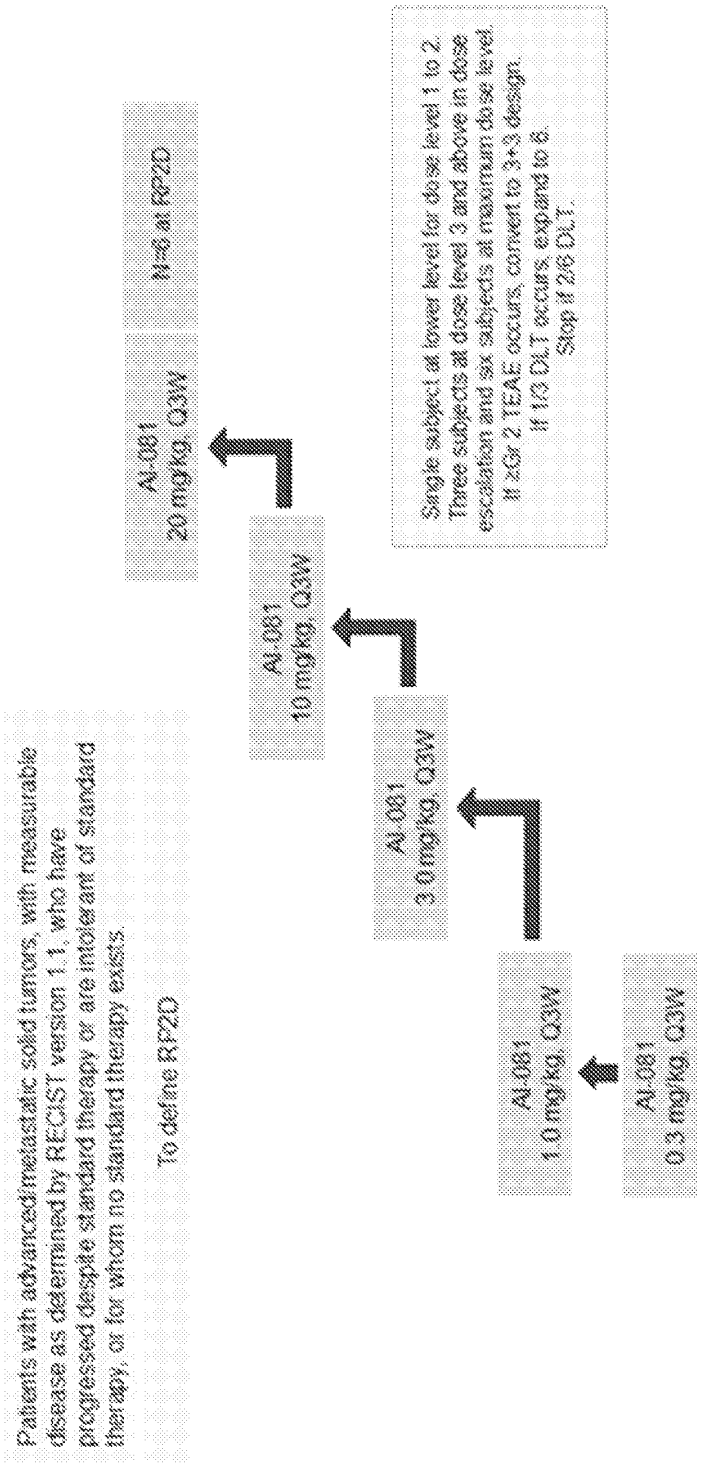

Patients with advanced/metastatic solid tumors, with measurable disease as determined by RECIST version 1.1, who have progressed despite standard therapy or are intolerant of standard therapy, or for whom no standard therapy exists.
To define RP2D
AJ-081 0.3 mg/kg, Q3W
AJ-081 1.0 mg/kg, Q3W
AJ-081 3.0 mg/kg, Q3W
AJ-081 10 mg/kg, Q3W
AJ-081 20 mg/kg, Q3W
N=6 at RP2D
Single subject at lower level for dose level 1 to 2. Three subjects at dose level 3 and above in dose escalation and six subjects at maximum dose level.
If ≥Gr 2 TEAE occurs, convert to 3+3 design.
If 1/3 DLT occurs, expand to 6.
Stop if 2/6 DLT.

FIG. 35

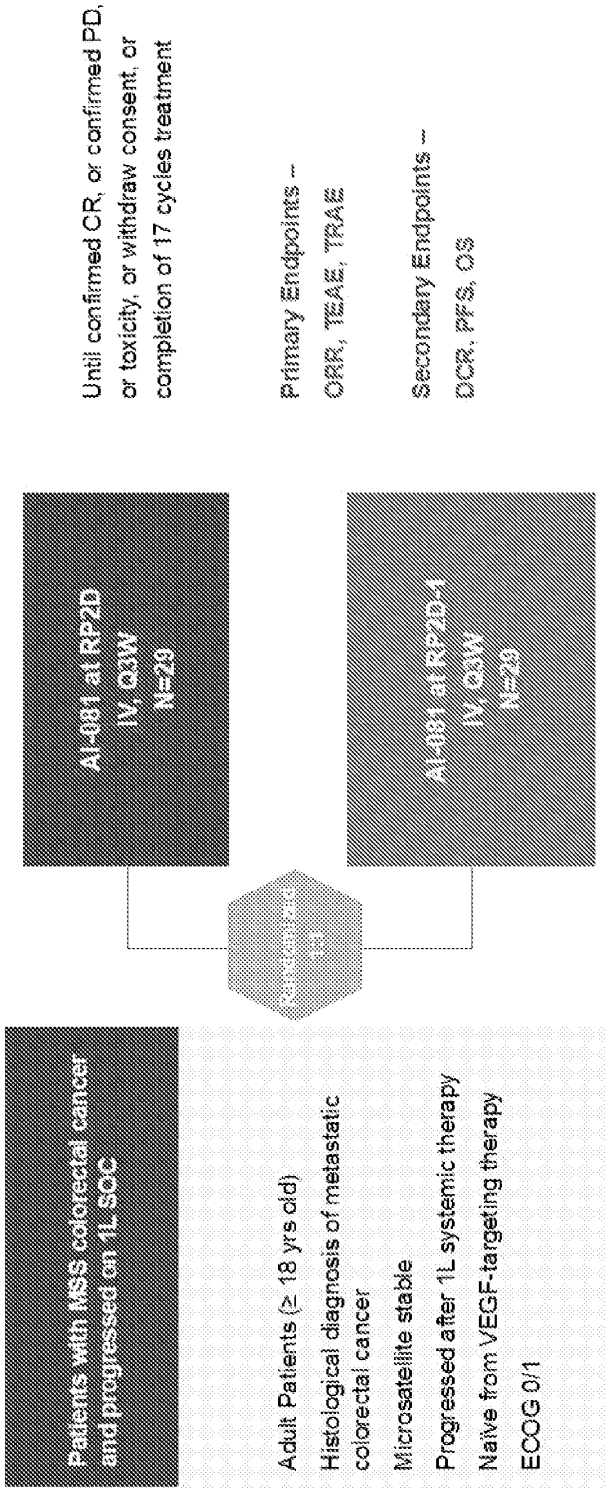

Patients with MSS colorectal cancer and progressed on 1L SOC
Adult Patients (≥ 18 yrs old)
Histological diagnosis of metastatic colorectal cancer
Microsatellite stable
Progressed after 1L systemic therapy
Naive from VEGF-targeting therapy
ECOG 0/1
Randomized 1:1
AI-081 at RP2D
IV, QxW
N=20
AI-081 at RP2D-1
IV, QxW
N=20
Until confirmed CR, or confirmed PD, or toxicity, or withdraw consent, or completion of 17 cycles treatment
Primary Endpoints –
ORR, TEAE, TRAE
Secondary Endpoints –
DCR, PFS, OS

FIG. 36

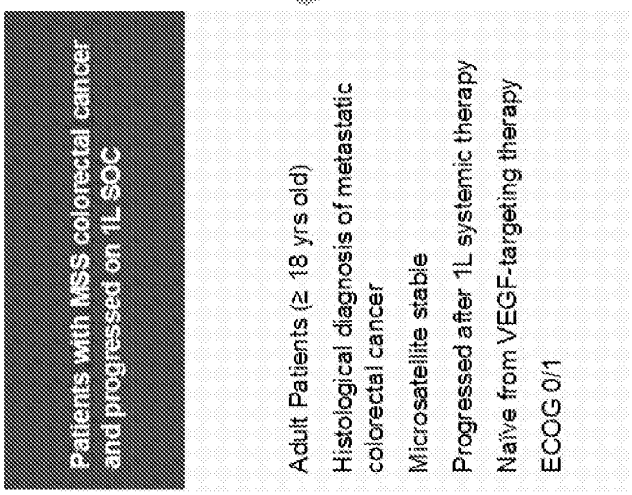
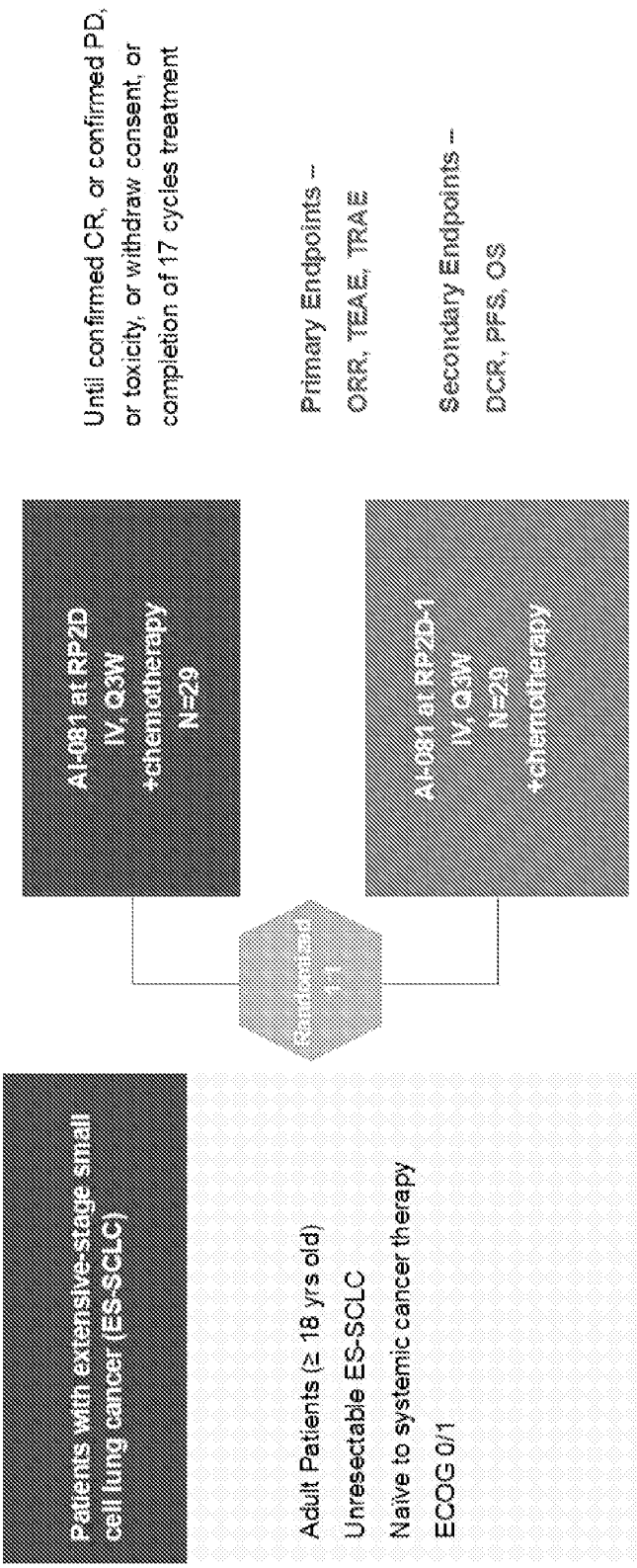

Patients with MSS colorectal cancer and progressed on 1L SOC
Adult Patients (≥ 18 yrs old)
Histological diagnosis of metastatic colorectal cancer
Microsatellite stable
Progressed after 1L systemic therapy
Naïve from VEGF-targeting therapy
ECOG 0/1
Randomization
AI-081 at RP2D
IV, Q3W
N=29
AI-081 at RP2D-1
IV, Q3W
N=29
Until confirmed CR, or confirmed PD, or toxicity, or withdraw consent, or completion of 17 cycles treatment
Primary Endpoints –
ORR, TEAE, TRAE
Secondary Endpoints –
DCR, PFS, OS

FIG. 37


Patients with extensive-stage small cell lung cancer (ES-SCLC)
Adult Patients (≥ 18 yrs old)
Unresectable ES-SCLC
Naive to systemic cancer therapy
ECOG 0/1
Randomization 1:1
AH081 at RP2D
IV, q3w
+chemotherapy
N=29
AH081 at RP2D-1
IV, q3w
N=29
+chemotherapy
Until confirmed CR, or confirmed PD, or toxicity, or withdraw consent, or completion of 17 cycles treatment
Primary Endpoints –
ORR, TEAE, TRAE
Secondary Endpoints –
DCR, PFS, OS