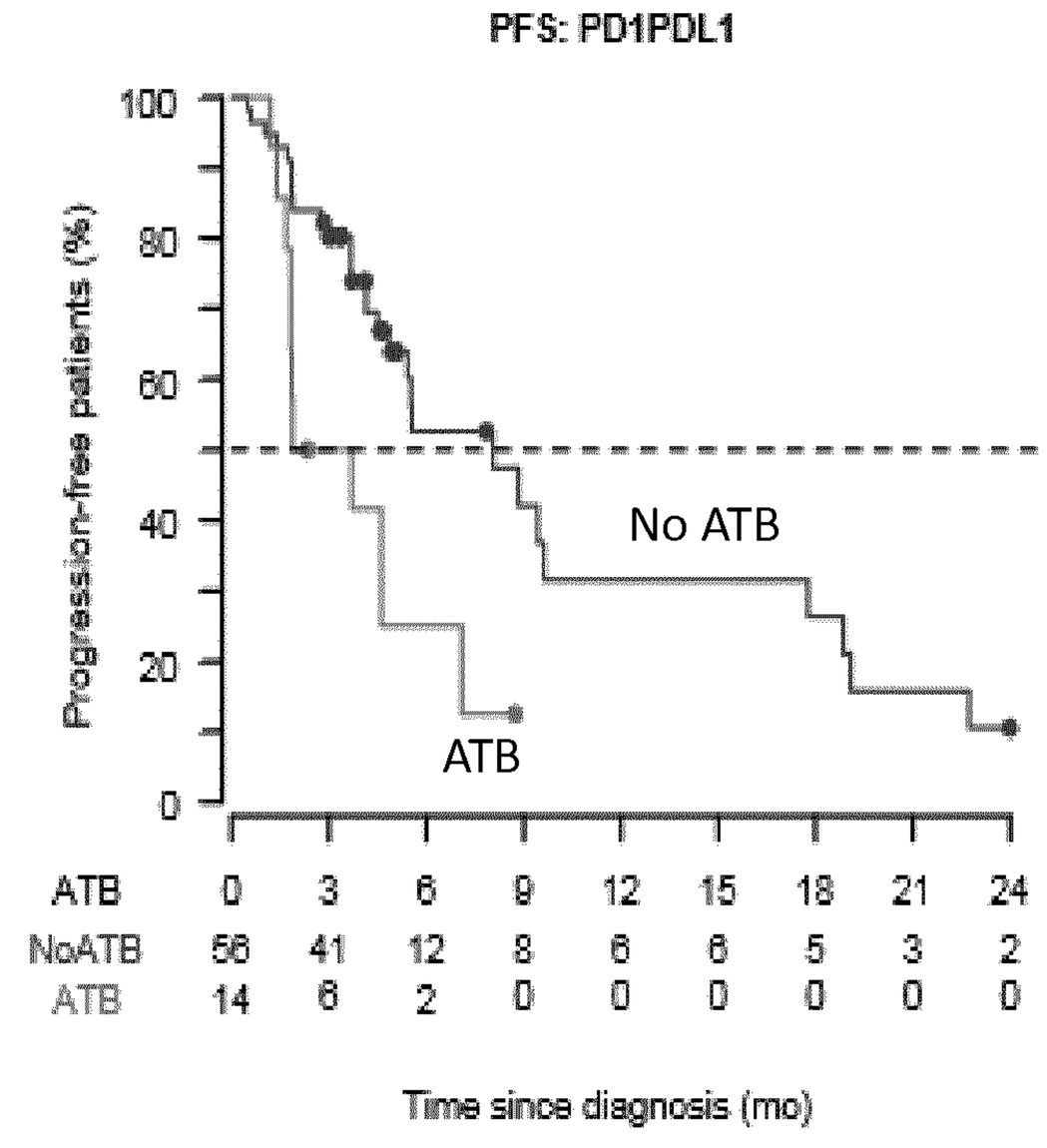
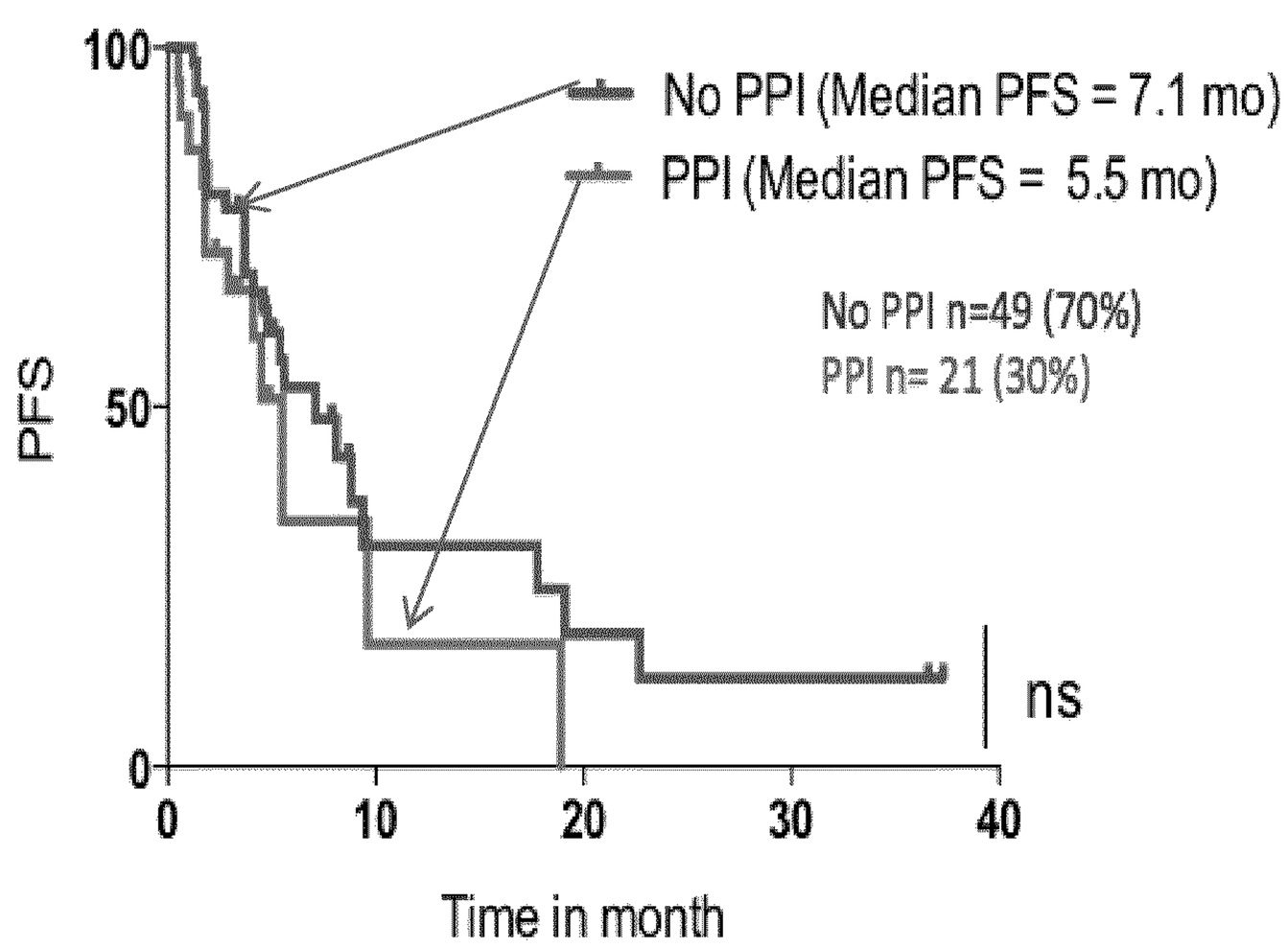

PFS: PD1PDL1
Progression-free patients (%)
100
80
60
40
20
0
No ATB
ATB
ATB 0 3 6 9 12 15 18 21 24
NoATB 56 41 12 8 6 6 5 3 2
ATB 14 6 2 0 0 0 0 0 0
Time since diagnosis (mo)

A


100
50
0
PFS
No PPI (Median PFS = 7.1 mo)
PPI (Median PFS = 5.5 mo)
No PPI n=49 (70%)
PPI n= 21 (30%)
ns
0
10
20
30
40
Time in month

B

Figure 1

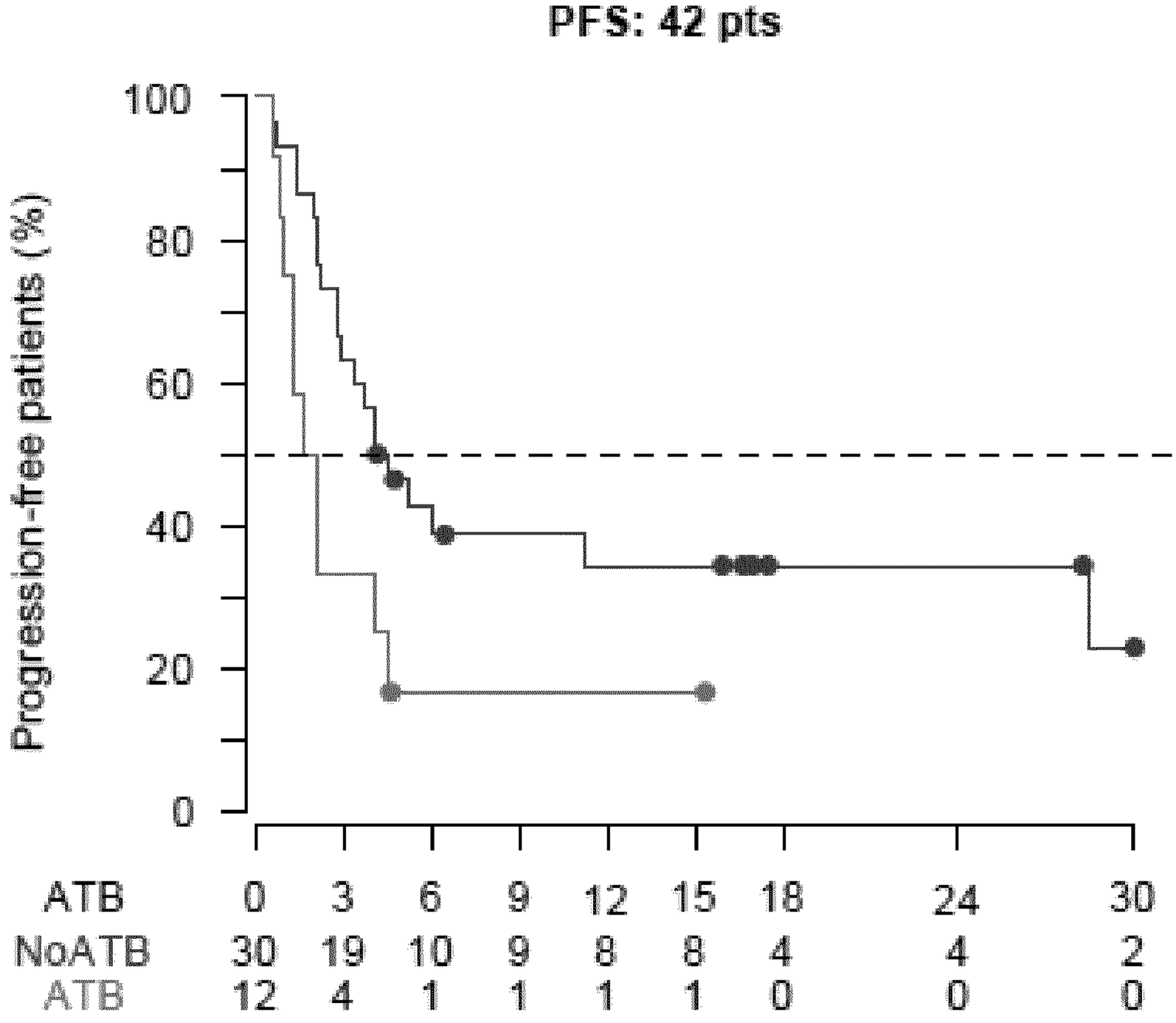

PFS: 42 pts
Progression-free patients (%)
100
80
60
40
20
0
ATB 0 3 6 9 12 15 18 24 30
NoATB 30 19 10 9 8 8 4 4 2
ATB 12 4 1 1 1 1 0 0 0
Time since first injection (mo)

Figure 2

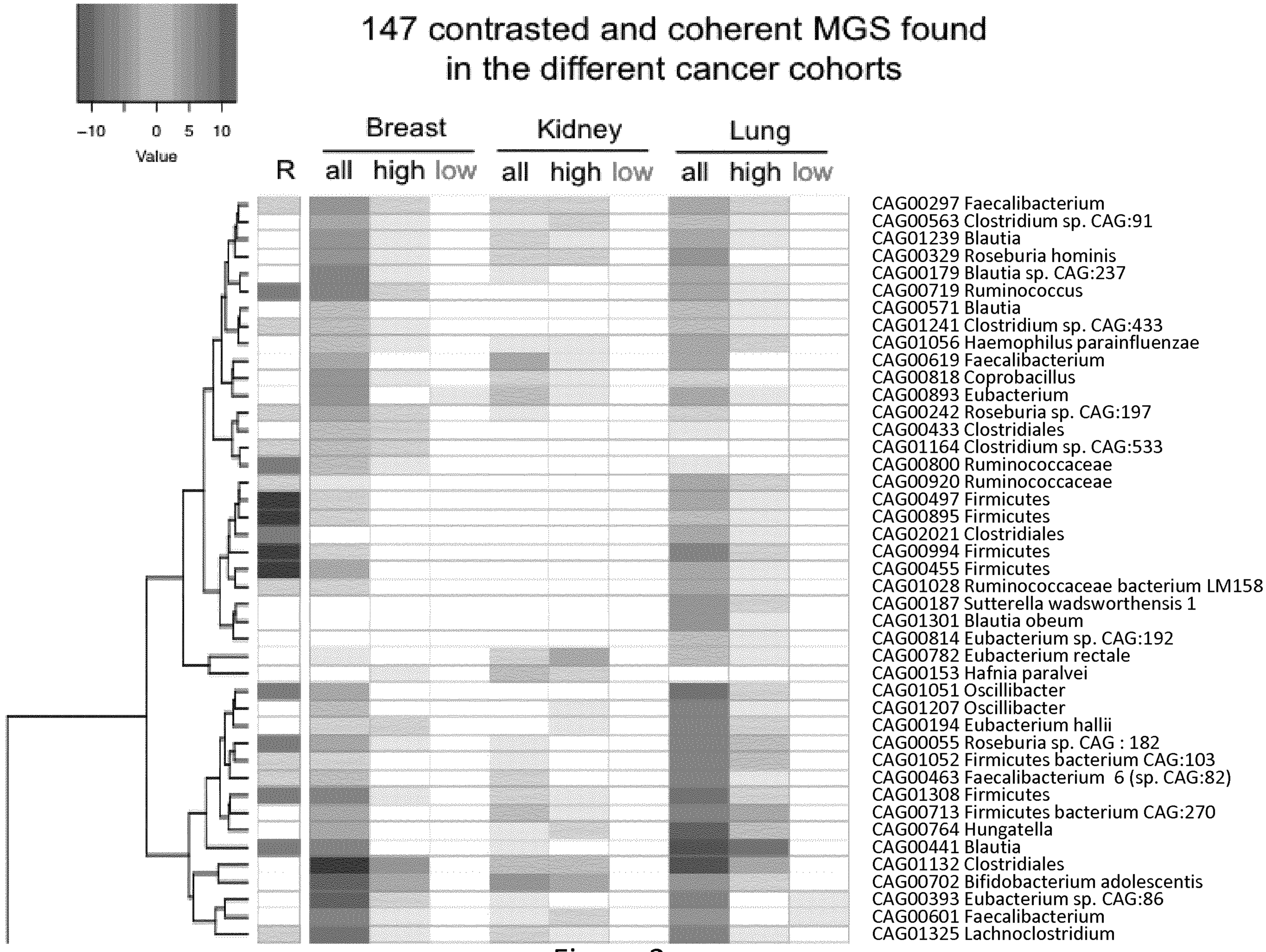

147 contrasted and coherent MGS found
in the different cancer cohorts
−10
0
5
10
Value
R
Breast
all
high
low
Kidney
all
high
low
Lung
all
high
low
CAG00297 Faecalibacterium
CAG00563 Clostridium sp. CAG:91
CAG01239 Blautia
CAG00329 Roseburia hominis
CAG00179 Blautia sp. CAG:237
CAG00719 Ruminococcus
CAG00571 Blautia
CAG01241 Clostridium sp. CAG:433
CAG01056 Haemophilus parainfluenzae
CAG00619 Faecalibacterium
CAG00818 Coprobacillus
CAG00893 Eubacterium
CAG00242 Roseburia sp. CAG:197
CAG00433 Clostridiales
CAG01164 Clostridium sp. CAG:533
CAG00800 Ruminococcaceae
CAG00920 Ruminococcaceae
CAG00497 Firmicutes
CAG00895 Firmicutes
CAG02021 Clostridiales
CAG00994 Firmicutes
CAG00455 Firmicutes
CAG01028 Ruminococcaceae bacterium LM158
CAG00187 Sutterella wadsworthensis 1
CAG01301 Blautia obeum
CAG00814 Eubacterium sp. CAG:192
CAG00782 Eubacterium rectale
CAG00153 Hafnia paralvei
CAG01051 Oscillibacter
CAG01207 Oscillibacter
CAG00194 Eubacterium hallii
CAG00055 Roseburia sp. CAG : 182
CAG01052 Firmicutes bacterium CAG:103
CAG00463 Faecalibacterium 6 (sp. CAG:82)
CAG01308 Firmicutes
CAG00713 Firmicutes bacterium CAG:270
CAG00764 Hungatella
CAG00441 Blautia
CAG01132 Clostridiales
CAG00702 Bifidobacterium adolescentis
CAG00393 Eubacterium sp. CAG:86
CAG00601 Faecalibacterium
CAG01325 Lachnoclostridium

Figure 3

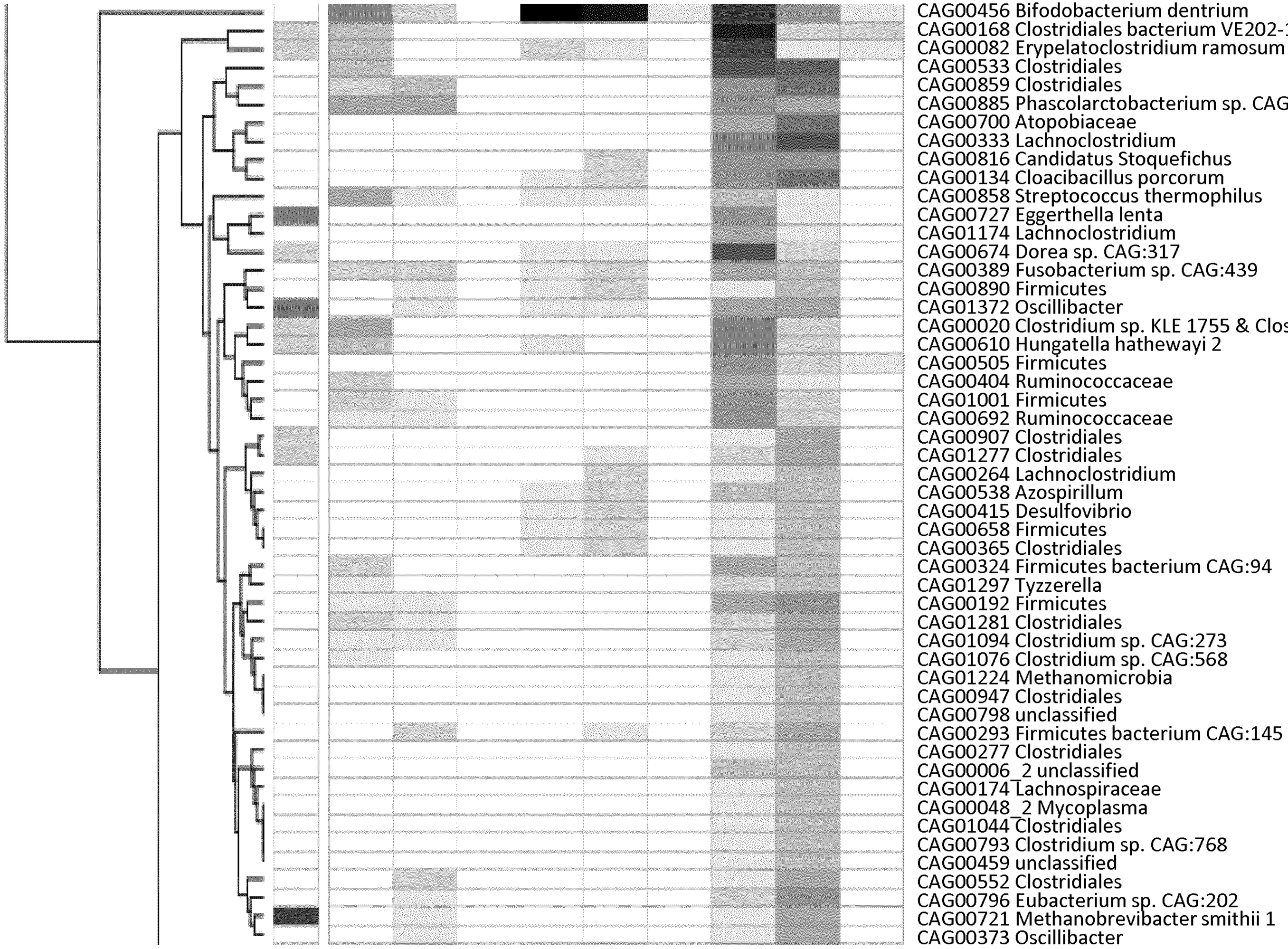


Figure 3 (follow-up)

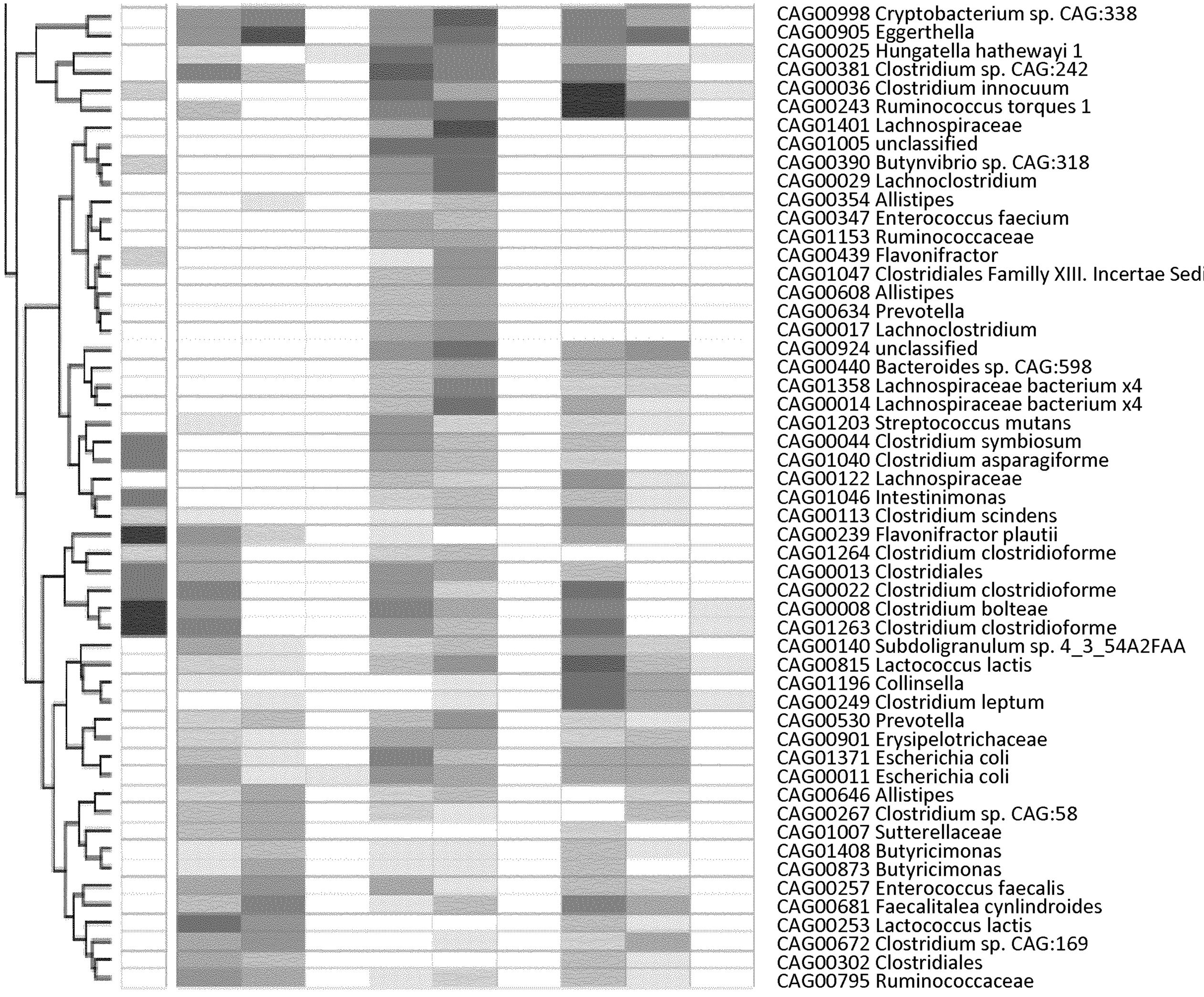


Figure 3 (follow-up)

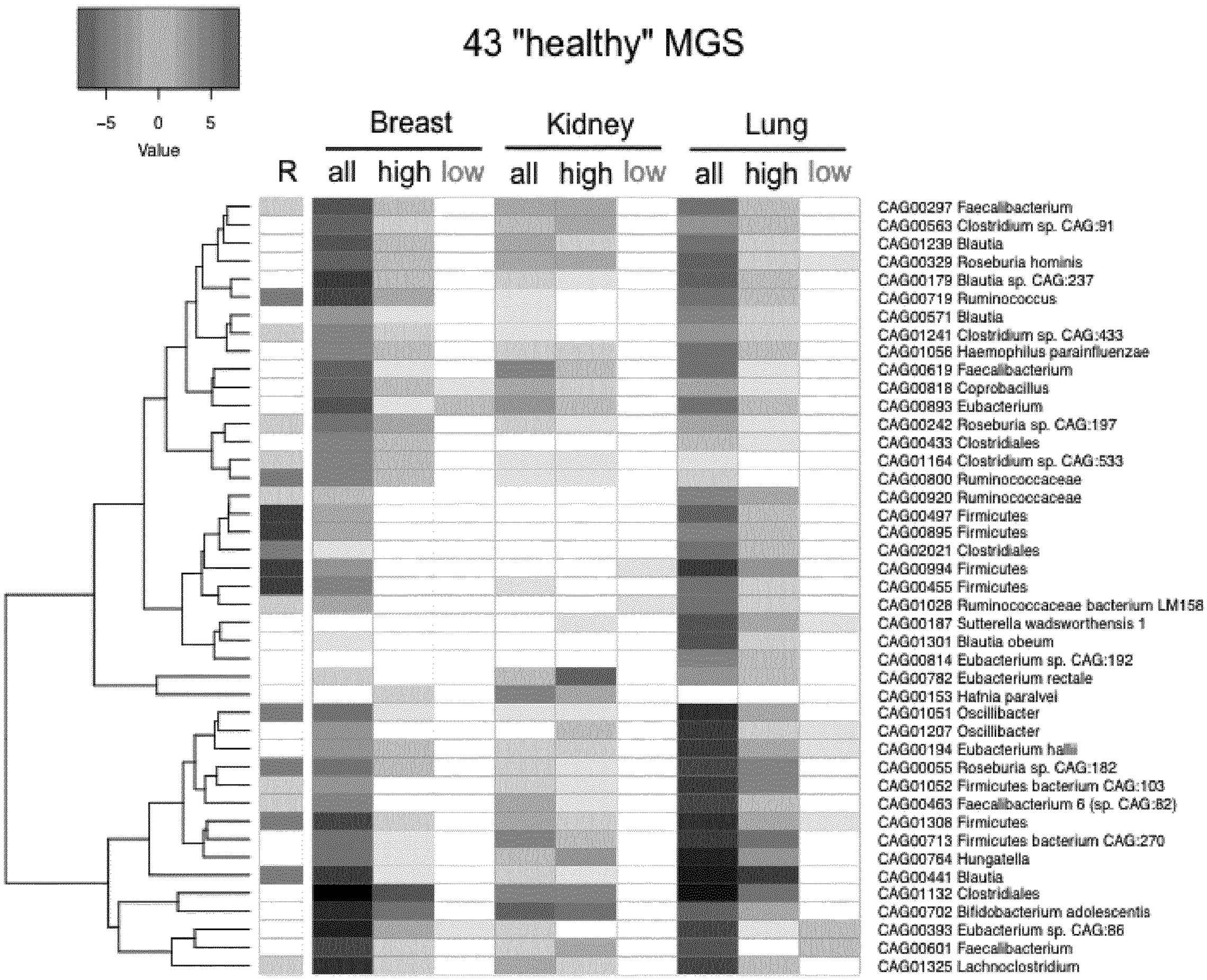

−5
0
5
Value
43 "healthy" MGS
Breast
Kidney
Lung
R
all
high
low
all
high
low
all
high
low
CAG00297 Faecalibacterium
CAG00563 Clostridium sp. CAG:91
CAG01239 Blautia
CAG00329 Roseburia hominis
CAG00179 Blautia sp. CAG:237
CAG00719 Ruminococcus
CAG00571 Blautia
CAG01241 Clostridium sp. CAG:433
CAG01056 Haemophilus parainfluenzae
CAG00619 Faecalibacterium
CAG00818 Coprobacillus
CAG00893 Eubacterium
CAG00242 Roseburia sp. CAG:197
CAG00433 Clostridiales
CAG01164 Clostridium sp. CAG:533
CAG00800 Ruminococcaceae
CAG00920 Ruminococcaceae
CAG00497 Firmicutes
CAG00895 Firmicutes
CAG02021 Clostridiales
CAG00994 Firmicutes
CAG00455 Firmicutes
CAG01028 Ruminococcaceae bacterium LM158
CAG00187 Sutterella wadsworthensis 1
CAG01301 Blautia obeum
CAG00814 Eubacterium sp. CAG:192
CAG00782 Eubacterium rectale
CAG00153 Hafnia paralvei
CAG01051 Oscillibacter
CAG01207 Oscillibacter
CAG00194 Eubacterium ha
CAG00055 Roseburia sp. CAG:182
CAG01052 Firmicutes bacterium CAG:103
CAG00463 Faecalibacterium 6 (sp. CAG:82)
CAG01308 Firmicutes
CAG00713 Firmicutes bacterium CAG:270
CAG00764 Hungatella
CAG00441 Blautia
CAG01132 Clostridiales
CAG00702 Bifidobacterium adolescentis
CAG00393 Eubacterium sp. CAG:86
CAG00601 Faecalibacterium
CAG01325 Lachnoclostridium

Figure 4

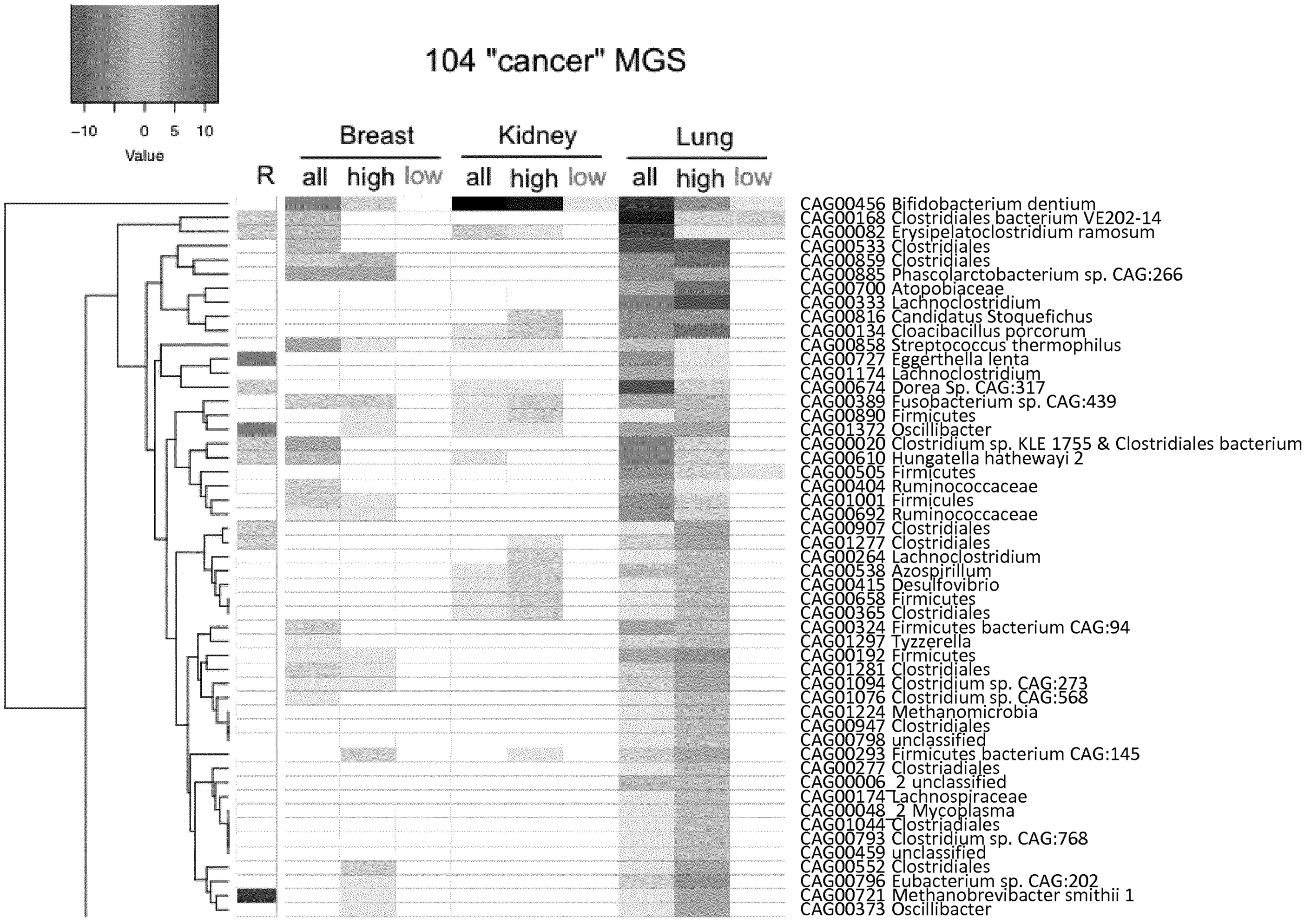

104 "cancer" MGS
−10
0
5
10
Value
Breast
Kidney
Lung
R
all
high
low
all
high
low
all
high
low
CAG00456 Bifidobacterium dentium
CAG00168 Clostridiales bacterium VE202-14
CAG00082 Erysipelatoclostridium ramosum
CAG00533 Clostridiales
CAG00859 Clostridiales
CAG00885 Phascolarctobacterium sp. CAG:266
CAG00700 Atopobiaceae
CAG00333 Lachnoclostridium
CAG00816 Candidatus Stoquefichus
CAG00134 Cloacibacillus porcorum
CAG00858 Streptococcus thermophilus
CAG00727 Eggerthella lenta
CAG01174 Lachnoclostridium
CAG00674 Dorea Sp. CAG:317
CAG00389 Fusobacterium sp. CAG:439
CAG00890 Firmicutes
CAG01372 Oscillibacter
CAG00020 Clostridium sp. KLE 1755 & Clostridiales bacterium
CAG00610 Hungatella hathewayi 2
CAG00505 Firmicutes
CAG00404 Ruminococcaceae
CAG01001 Firmicules
CAG00692 Ruminococcaceae
CAG00907 Clostridiales
CAG01277 Clostridiales
CAG00264 Lachnoclostridium
CAG00538 Azospirillum
CAG00415 Desulfovibrio
CAG00658 Firmicutes
CAG00365 Clostridiales
CAG00324 Firmicutes bacterium CAG:94
CAG01297 Tyzzerella
CAG00192 Firmicutes
CAG01281 Clostridiales
CAG01094 Clostridium sp. CAG:273
CAG01076 Clostridium sp. CAG:568
CAG01224 Methanomicrobia
CAG00947 Clostridiales
CAG00798 unclassified
CAG00293 Firmicutes bacterium CAG:145
CAG00277 Clostridiales
CAG00006_2 unclassified
CAG00174 Lachnospiraceae
CAG00048_2 Mycoplasma
CAG01044 Clostridiales
CAG00793 Clostridium sp. CAG:768
CAG00459 unclassified
CAG00552 Clostridiales
CAG00796 Eubacterium sp. CAG:202
CAG00721 Methanobrevibacter smithii 1
CAG00373 Oscillibacter

Figure 5

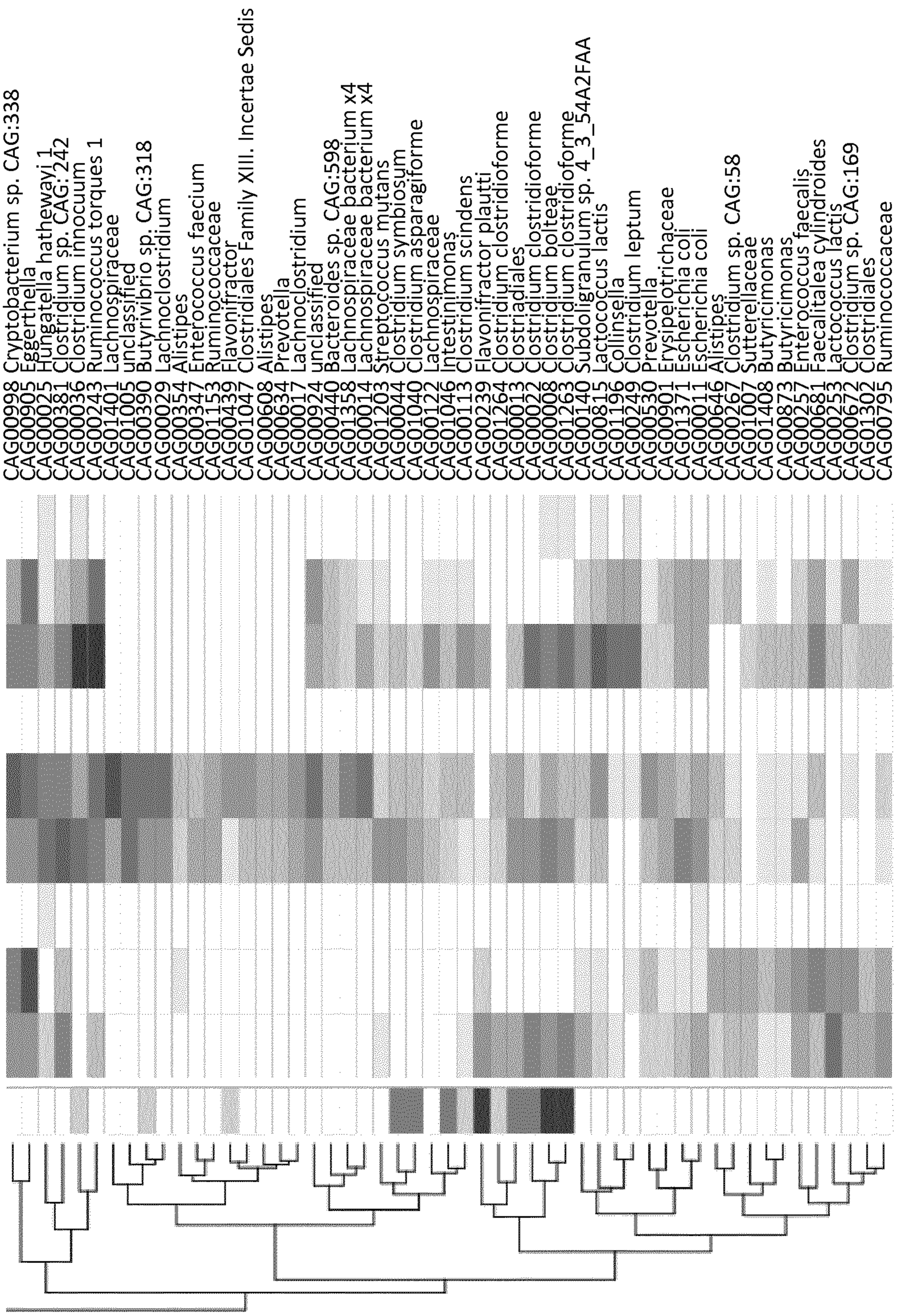


Figure 5 (follow-up)

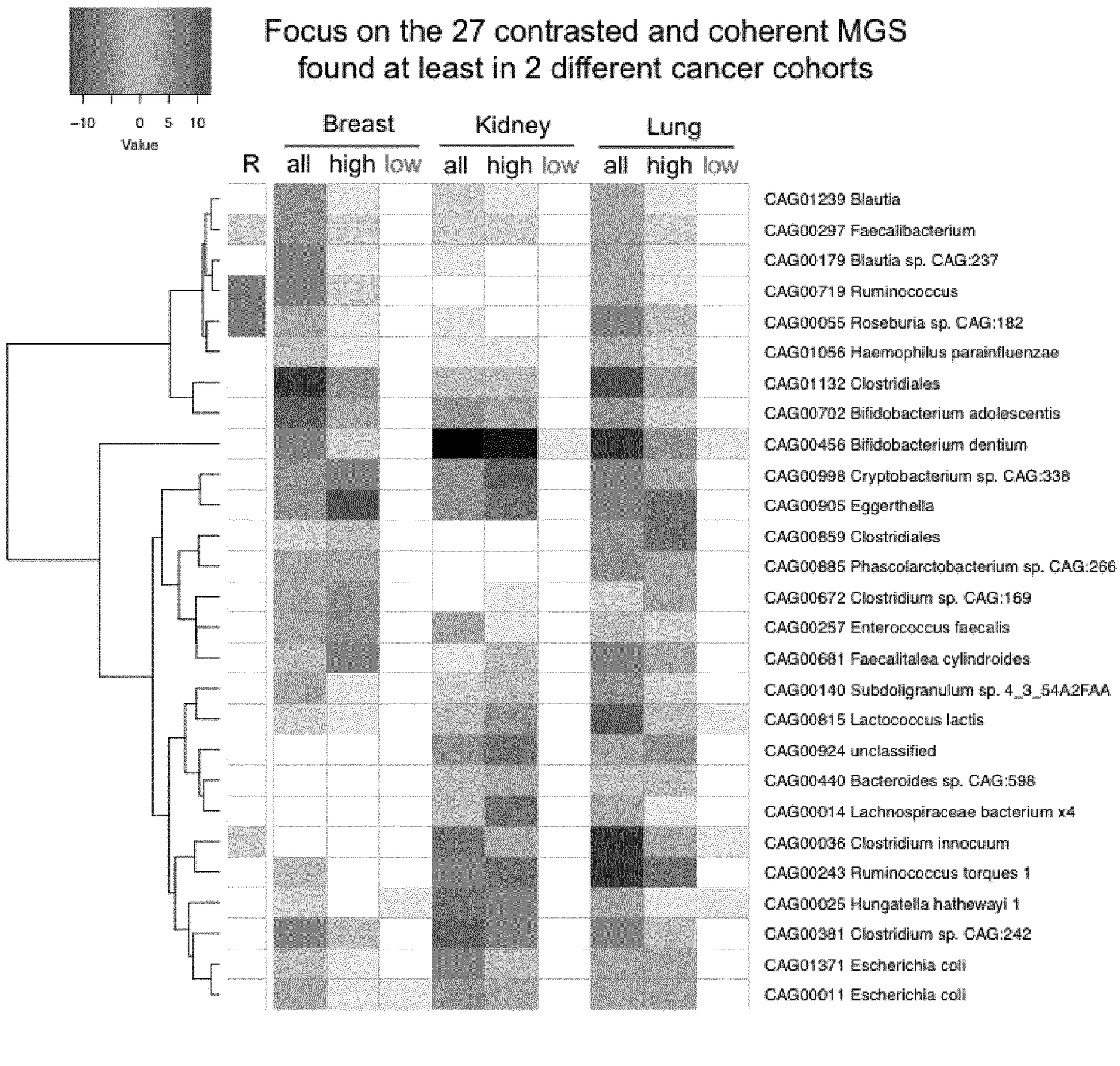

Focus on the 27 contrasted and coherent MGS found at least in 2 different cancer cohorts
−10
0
5
10
Value
Breast
Kidney
Lung
R
all
high
low
all
high
low
all
high
low
CAG01239 Blautia
CAG00297 Faecalibacterium
CAG00179 Blautia sp. CAG:237
CAG00719 Ruminococcus
CAG00055 Roseburia sp. CAG:182
CAG01056 Haemophilus parainfluenzae
CAG01132 Clostridiales
CAG00702 Bifidobacterium adolescentis
CAG00456 Bifidobacterium dentium
CAG00998 Cryptobacterium sp. CAG:338
CAG00905 Eggerthella
CAG00859 Clostridiales
CAG00885 Phascolarctobacterium sp. CAG:266
CAG00672 Clostridium sp. CAG:169
CAG00257 Enterococcus faecalis
CAG00681 Faecalitalea cylindroides
CAG00140 Subdoligranulum sp. 4_3_54A2FAA
CAG00815 Lactococcus lactis
CAG00924 unclassified
CAG00440 Bacteroides sp. CAG:598
CAG00014 Lachnospiraceae bacterium x4
CAG00036 Clostridium innocuum
CAG00243 Ruminococcus torques 1
CAG00025 Hungatella hathewayi 1
CAG00381 Clostridium sp. CAG:242
CAG01371 Escherichia coli
CAG00011 Escherichia coli

Figure 6

H

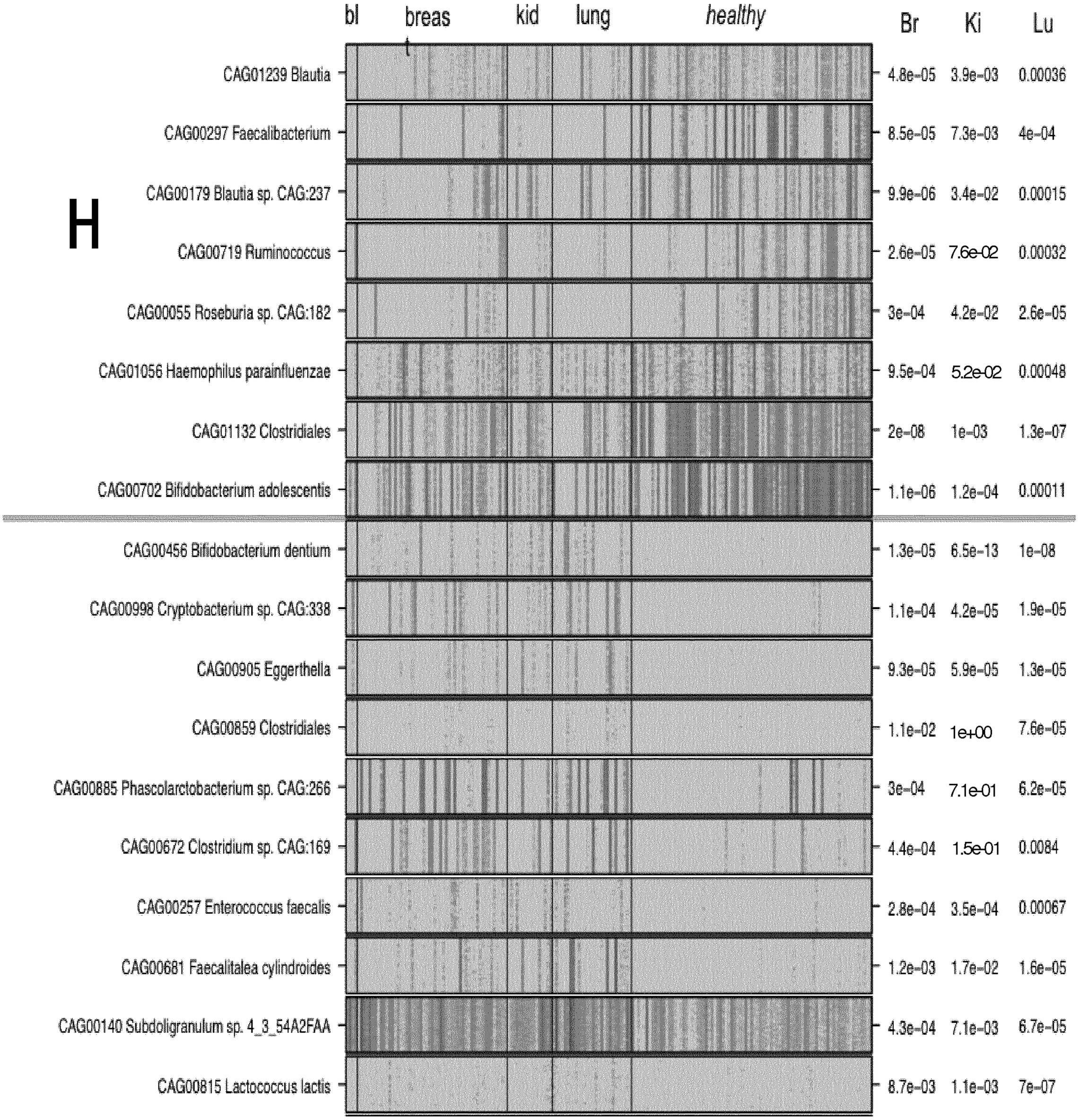

bl
breas
kid
lung
healthy
Br
Ki
Lu
CAG01239 Blautia
4.8e-05 3.9e-03 0.00036
CAG00297 Faecalibacterium
8.5e-05 7.3e-03 4e-04
CAG00179 Blautia sp. CAG:237
9.9e-06 3.4e-02 0.00015
CAG00719 Ruminococcus
2.6e-05 7.6e-02 0.00032
CAG00055 Roseburia sp. CAG:182
3e-04 4.2e-02 2.6e-05
CAG01056 Haemophilus parainfluenzae
9.5e-04 5.2e-02 0.00048
CAG01132 Clostridiales
2e-08 1e-03 1.3e-07
CAG00702 Bifidobacterium adolescentis
1.1e-06 1.2e-04 0.00011
CAG00456 Bifidobacterium dentium
1.3e-05 6.5e-13 1e-08
CAG00998 Cryptobacterium sp. CAG:338
1.1e-04 4.2e-05 1.9e-05
CAG00905 Eggerthella
9.3e-05 5.9e-05 1.3e-05
CAG00859 Clostridiales
1.1e-02 1e+00 7.6e-05
CAG00885 Phascolarctobacterium sp. CAG:266
3e-04 7.1e-01 6.2e-05
CAG00672 Clostridium sp. CAG:169
4.4e-04 1.5e-01 0.0084
CAG00257 Enterococcus faecalis
2.8e-04 3.5e-04 0.00067
CAG00681 Faecalitalea cylindroides
1.2e-03 1.7e-02 1.6e-05
CAG00140 Subdoligranulum sp. 4_3_54A2FAA
4.3e-04 7.1e-03 6.7e-05
CAG00815 Lactococcus lactis
8.7e-03 1.1e-03 7e-07

Figure 7

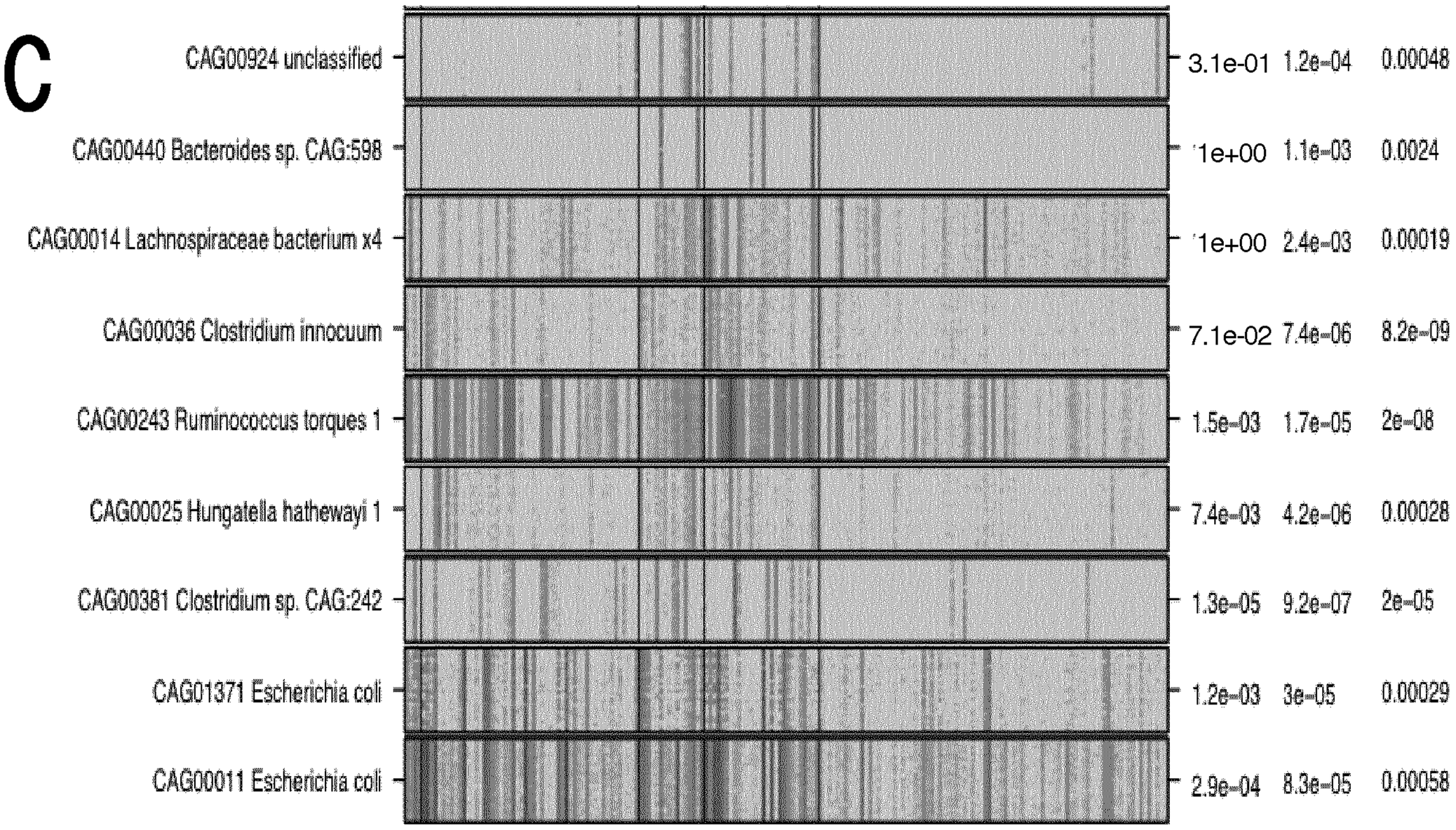


Figure 7 (follow-up)

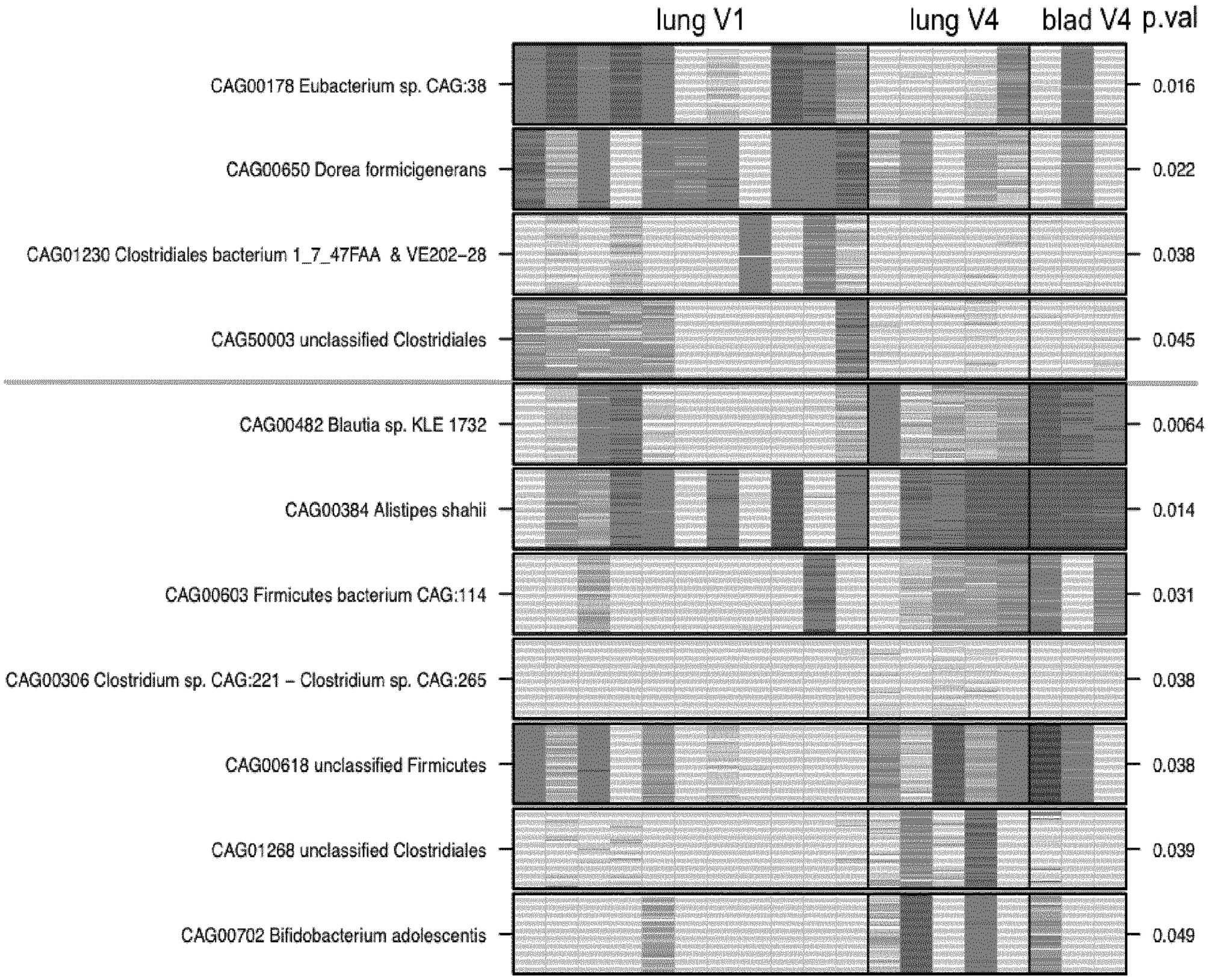

lung V1
lung V4
blad V4
p.val
CAG00178 Eubacterium sp. CAG:38
0.016
CAG00650 Dorea formicigenerans
0.022
CAG01230 Clostridiales bacterium 1_7_47FAA & VE202-28
0.038
CAG50003 unclassified Clostridiales
0.045
CAG00482 Blautia sp. KLE 1732
0.0064
CAG00384 Alistipes shahii
0.014
CAG00603 Firmicutes bacterium CAG:114
0.031
CAG00306 Clostridium sp. CAG:221 – Clostridium sp. CAG:265
0.038
CAG00618 unclassified Firmicutes
0.038
CAG01268 unclassified Clostridiales
0.039
CAG00702 Bifidobacterium adolescentis
0.049

Figure 8

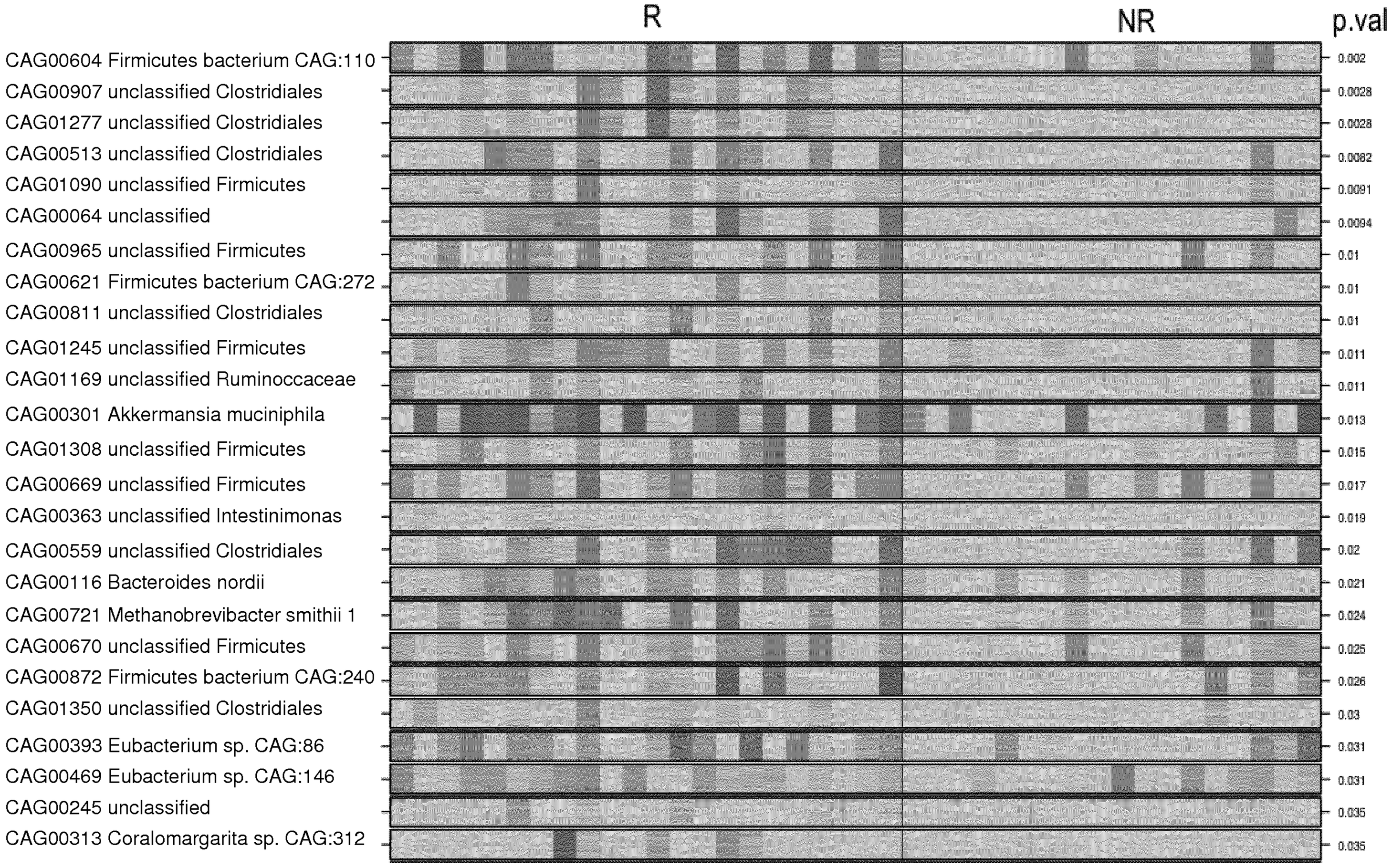

R
NR
p.val
CAG00604 Firmicutes bacterium CAG:110
CAG00907 unclassified Clostridiales
CAG01277 unclassified Clostridiales
CAG00513 unclassified Clostridiales
CAG01090 unclassified Firmicutes
CAG00064 unclassified
CAG00965 unclassified Firmicutes
CAG00621 Firmicutes bacterium CAG:272
CAG00811 unclassified Clostridiales
CAG01245 unclassified Firmicutes
CAG01169 unclassified Ruminoccaceae
CAG00301 Akkermansia muciniphila
CAG01308 unclassified Firmicutes
CAG00669 unclassified Firmicutes
CAG00363 unclassified Intestinimonas
CAG00559 unclassified Clostridiales
CAG00116 Bacteroides nordii
CAG00721 Methanobrevibacter smithii 1
CAG00670 unclassified Firmicutes
CAG00872 Firmicutes bacterium CAG:240
CAG01350 unclassified Clostridiales
CAG00393 Eubacterium sp. CAG:86
CAG00469 Eubacterium sp. CAG:146
CAG00245 unclassified
CAG00313 Coralomargarita sp. CAG:312
0.002
0.0028
0.0028
0.0082
0.0091
0.0094
0.01
0.01
0.01
0.011
0.011
0.013
0.015
0.017
0.019
0.02
0.021
0.024
0.025
0.026
0.03
0.031
0.031
0.035
0.035

Figure 9

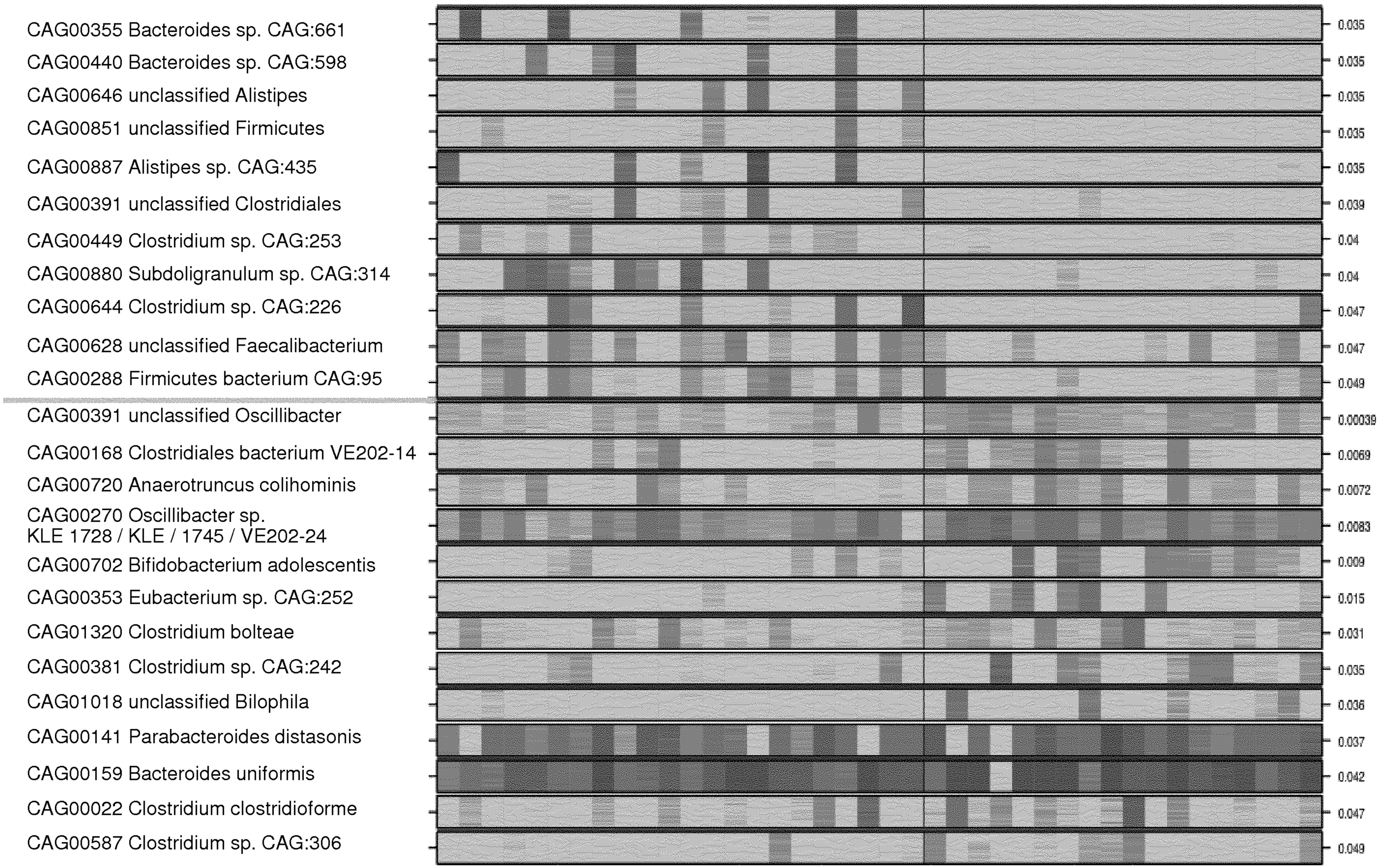


Figure 9 (follow-up)

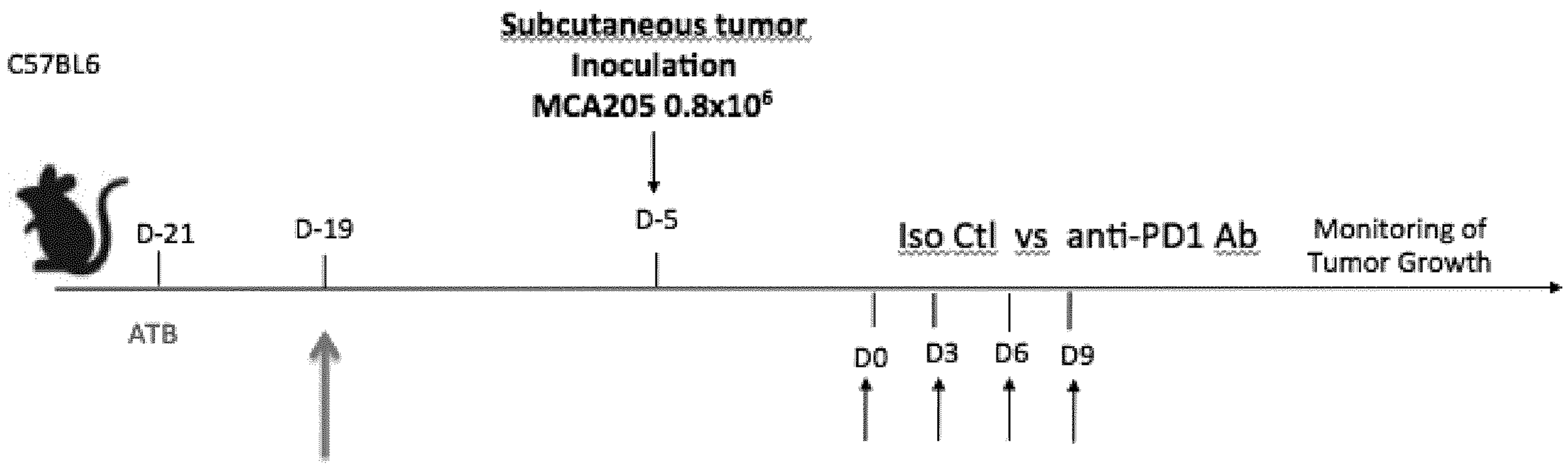
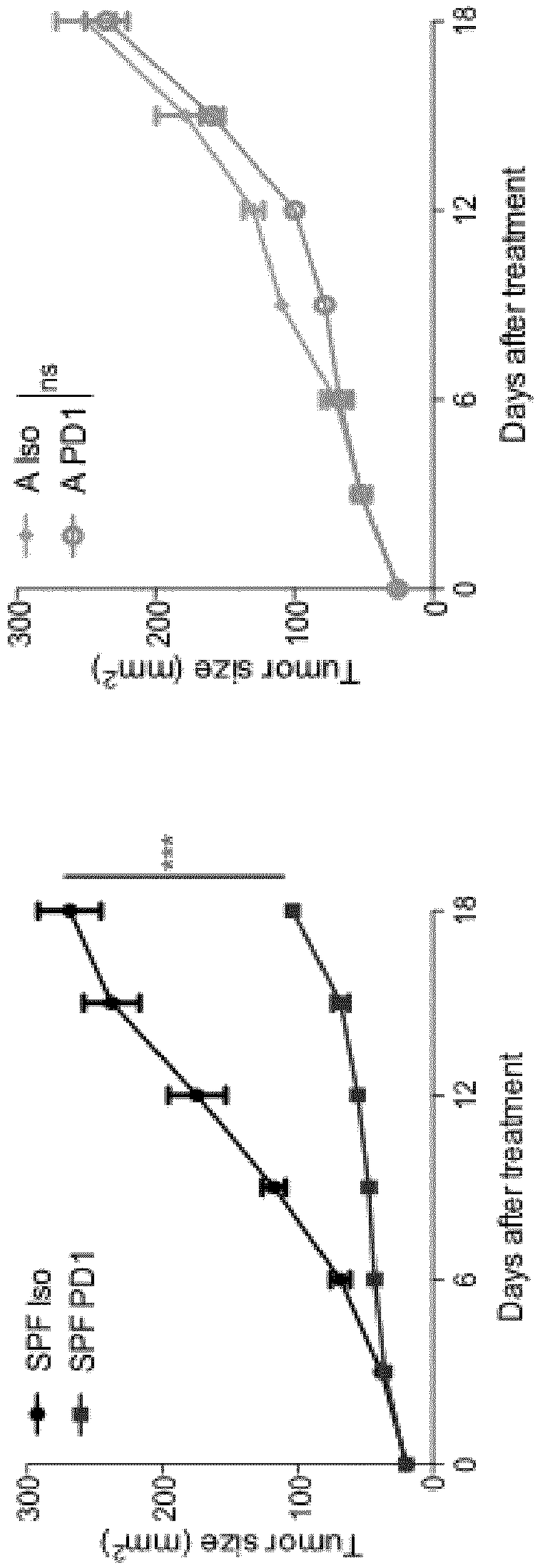
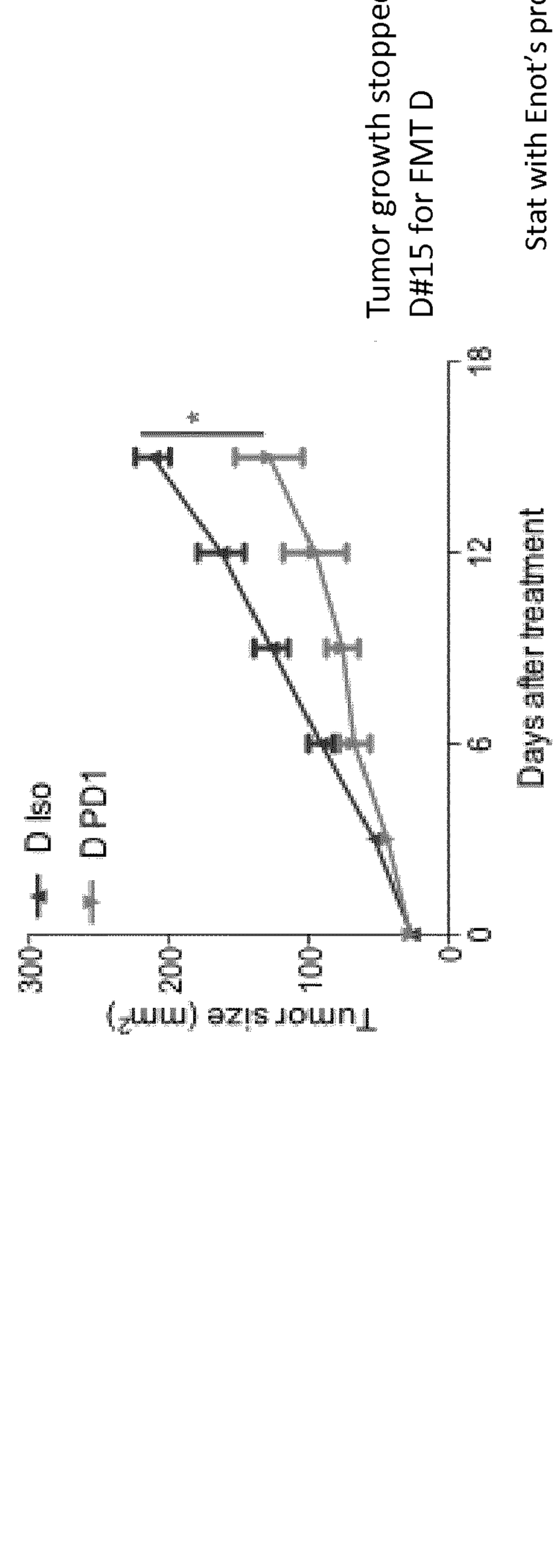

C57BL6
Subcutaneous tumor
Inoculation
MCA205 0.8x10⁶
D-21
D-19
D-5
Iso Ctl vs anti-PD1 Ab
Monitoring of
Tumor Growth
ATB
D0
D3
D6
D9
FMT
1. NaCl
2. A: Progression
3. B: Progression
4. E: Progression
5. F: Progression
6. C: Responder: Partial Response
7. D: Responder: Partial Response
14 mice/FMT, 7 mice/ group

Figure 10

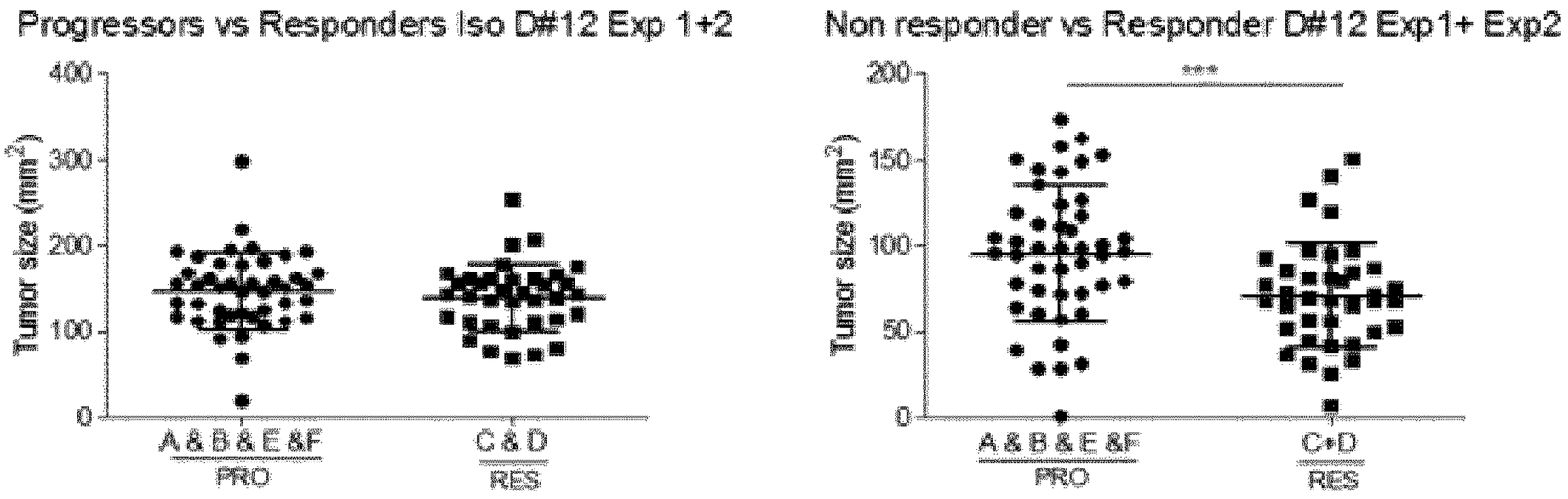




Tumor growth stopped at D#15 for FMT D

Stat with Enot's program

Figure 11



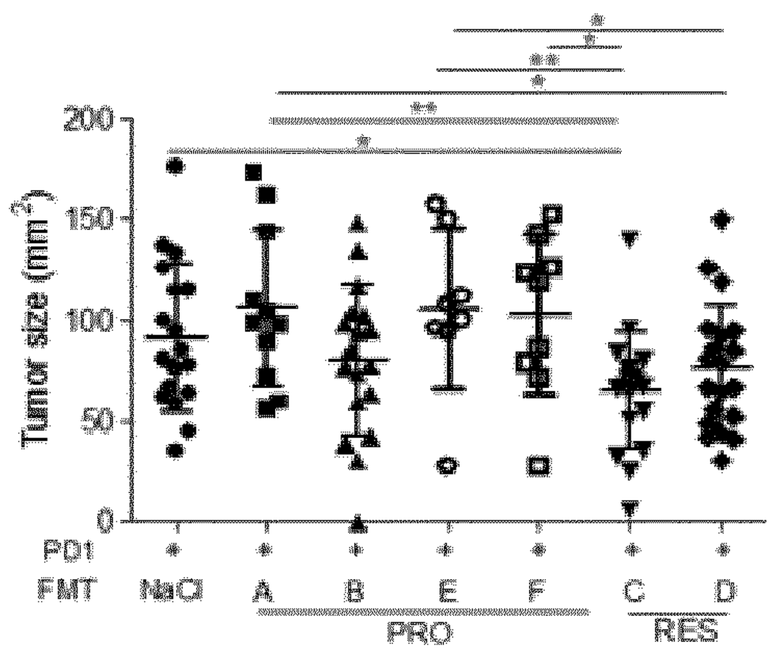
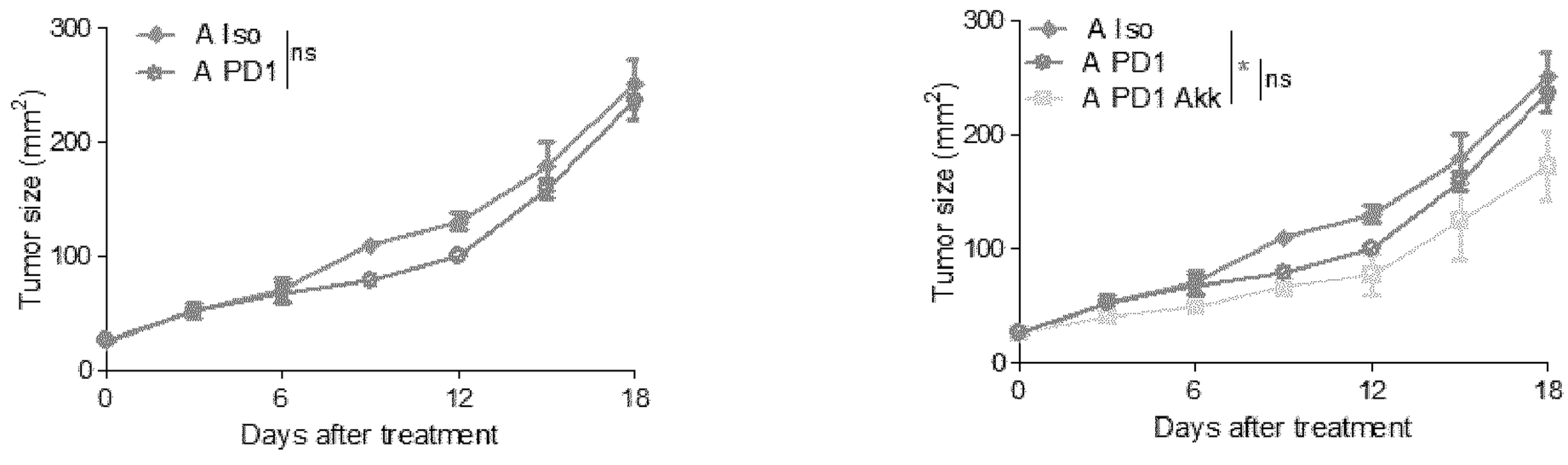


Figure 12



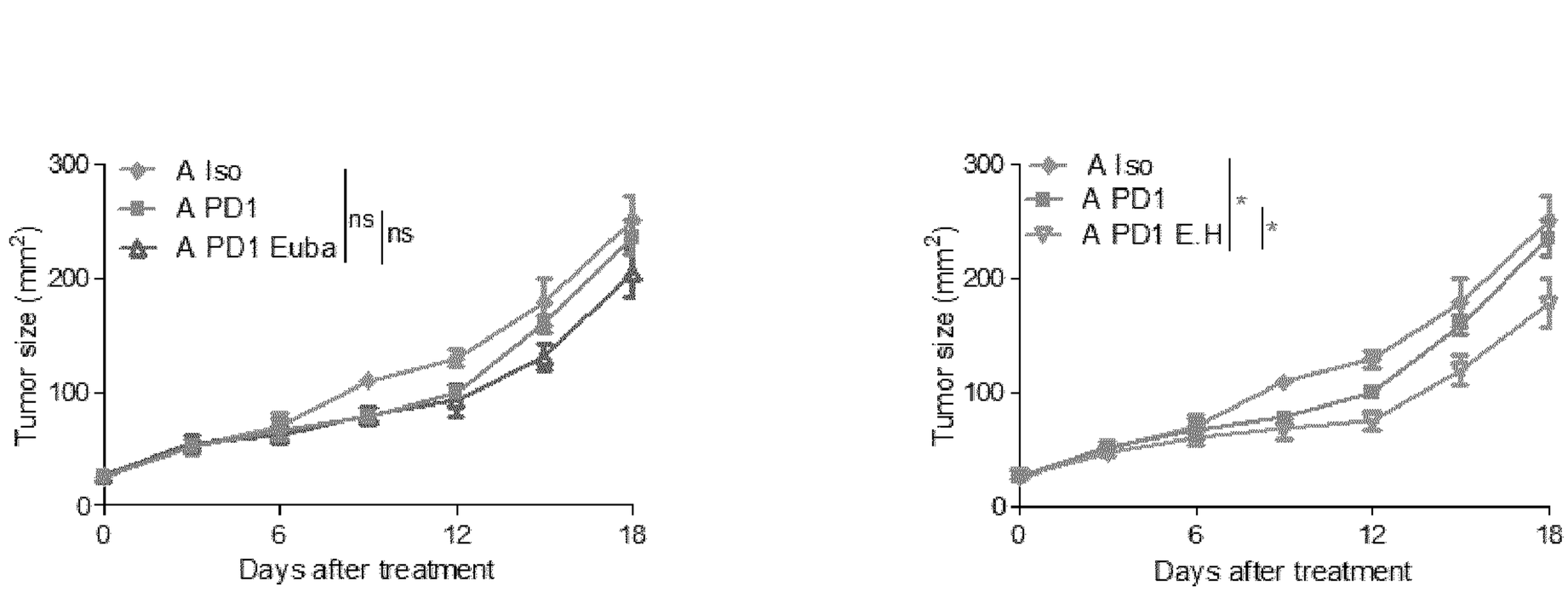


Figure 13

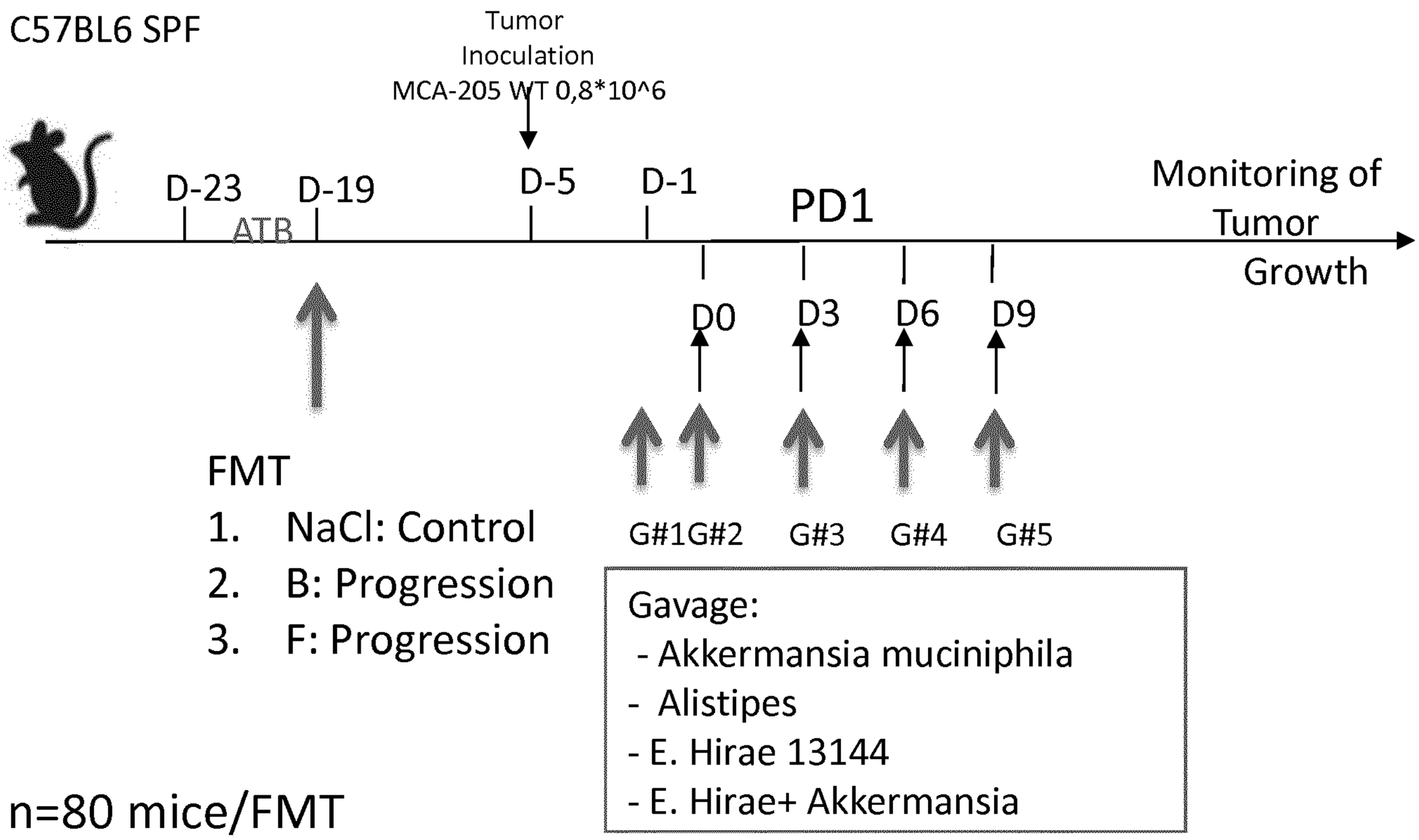


Figure 14

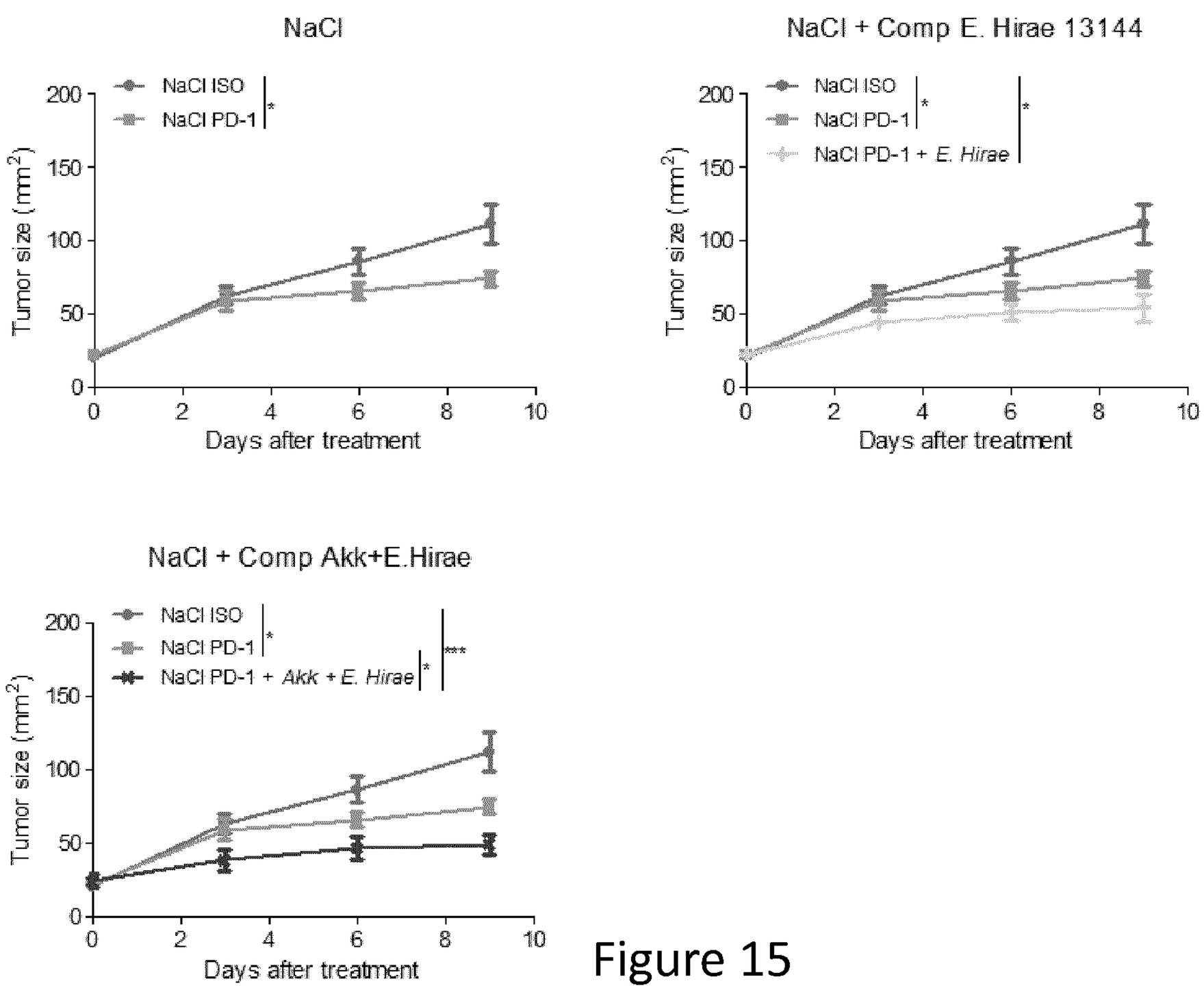


Figure 15

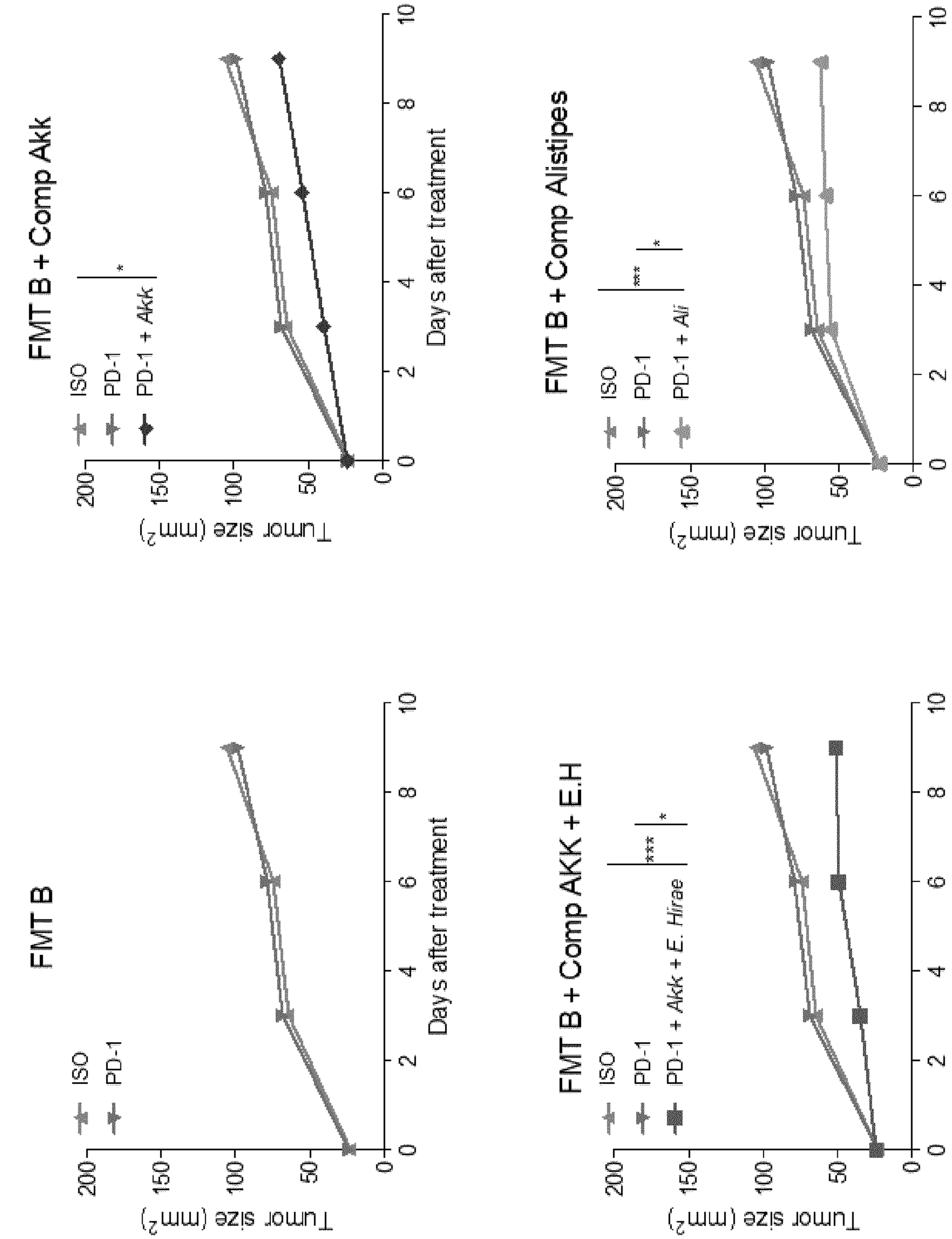
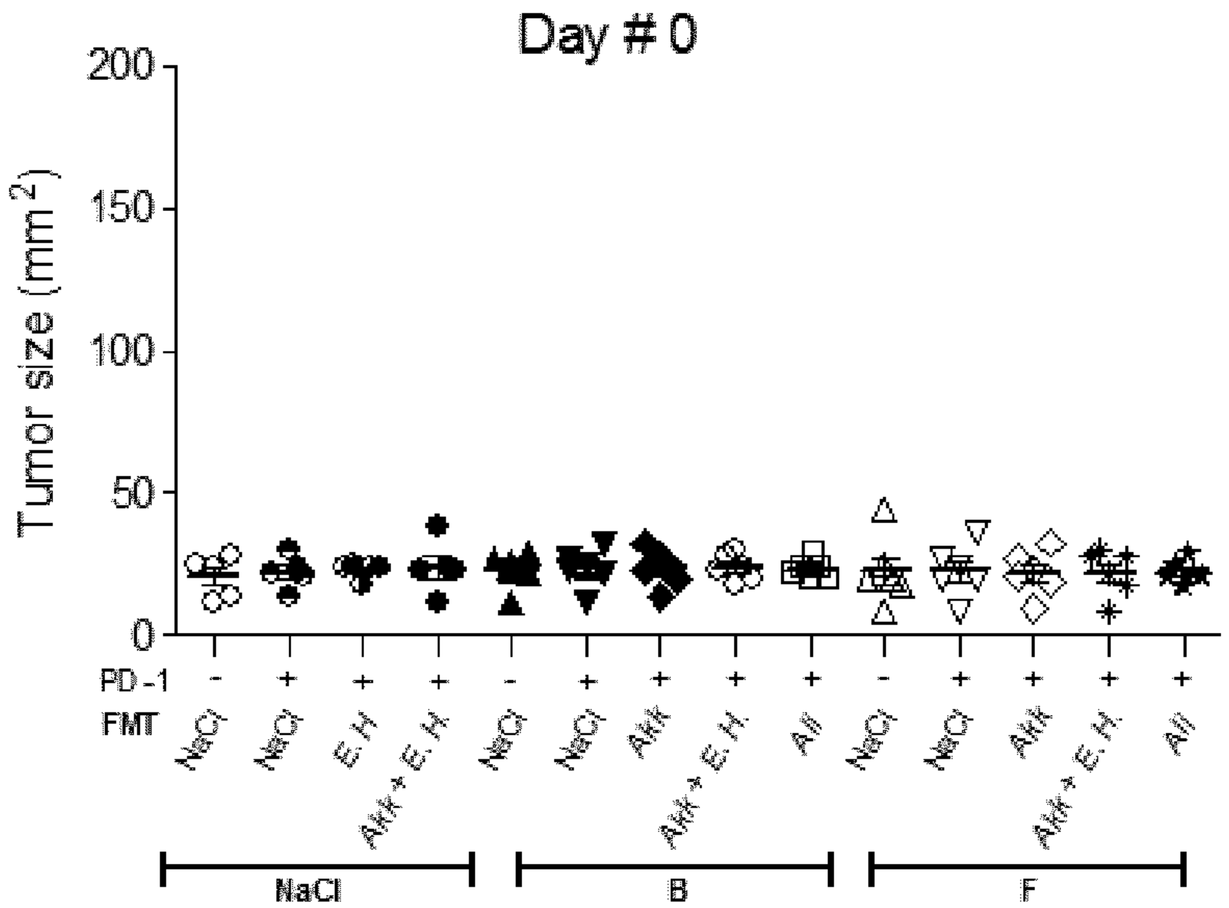
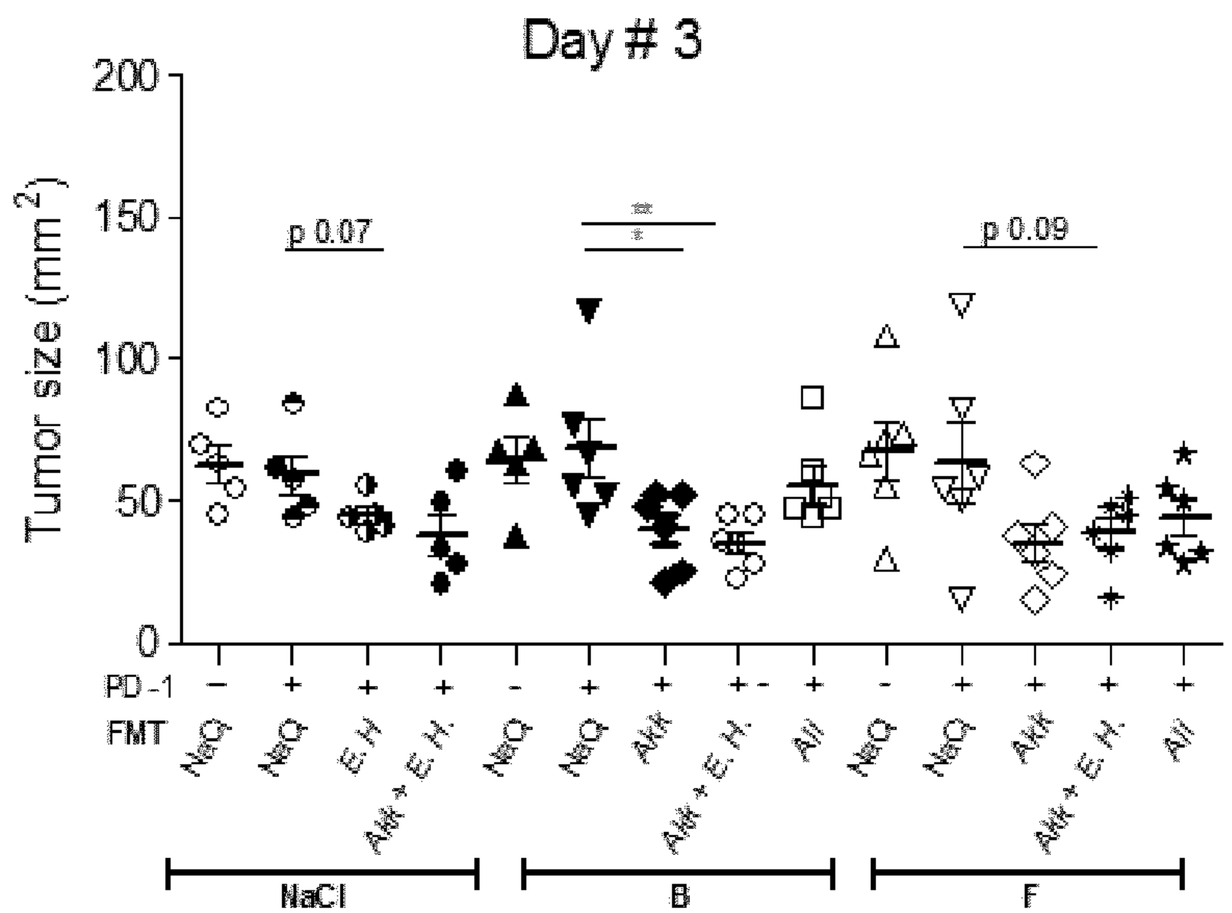
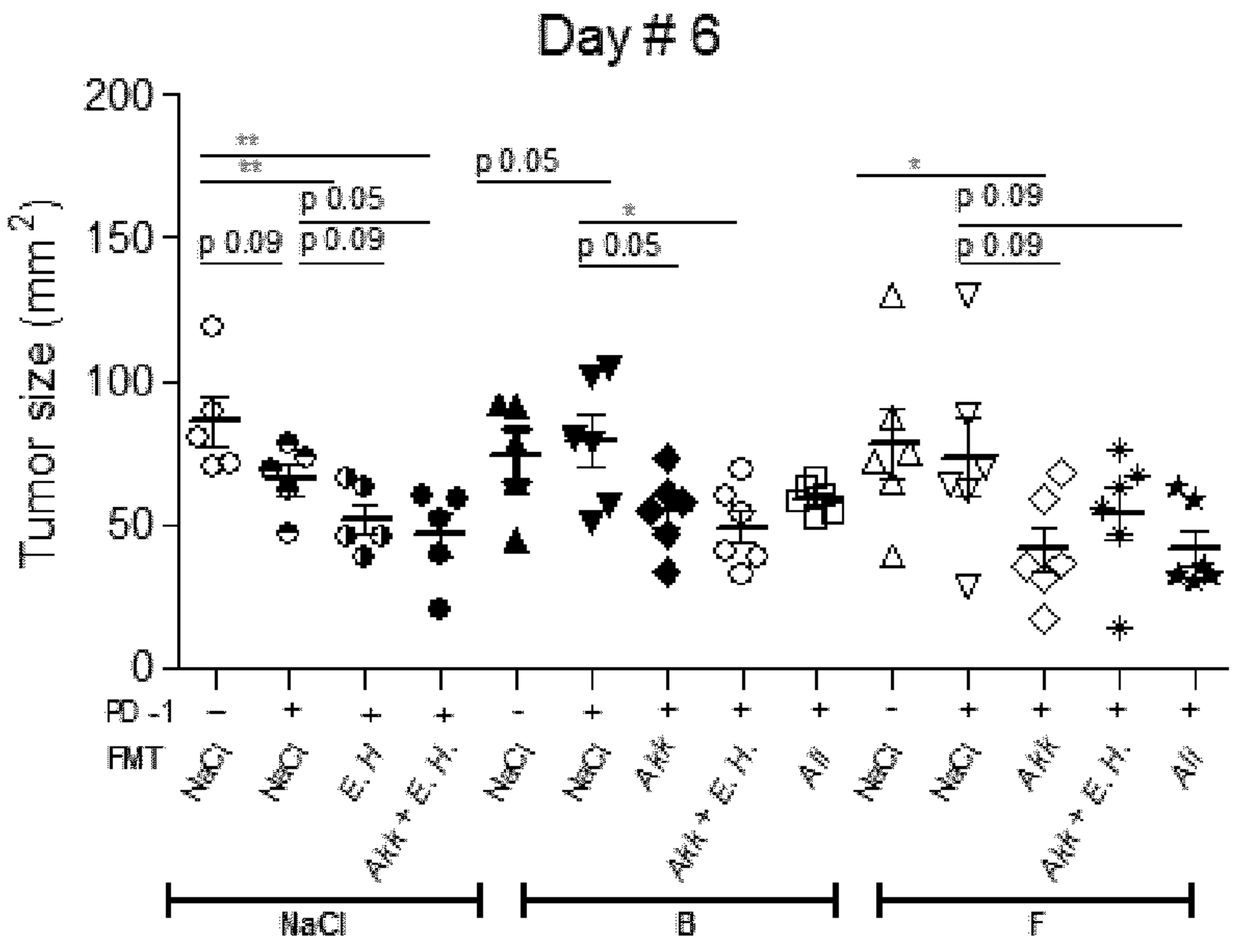

FMT B
ISO
PD-1
Tumor size (mm²)
Days after treatment
FMT B + Comp Akk
PD-1 + Akk
*
FMT B + Comp Alistipes
PD-1 + Ali
***
FMT B + Comp AKK + E.H
PD-1 + Akk + E. Hirae

Figure 16


Day # 0
Tumor size (mm 2)
200
150
100
50
0
PD-1
FMT
NaCl
NaCl
E. H
Akk + E. H.
NaCl
NaCl
Akk
Akk + E. H.
All
NaCl
NaCl
Akk
Akk + E. H.
All
NaCl
B
F


Day # 3
Tumor size (mm 2)
200
150
100
50
0
p 0.07
p 0.09
PD-1
FMT
NaCl
NaCl
E. H
Akk + E. H.
NaCl
NaCl
Akk
Akk + E. H.
All
NaCl
NaCl
Akk
Akk + E. H.
All
NaCl
B
F


Day # 6
Tumor size (mm 2)
200
150
100
50
0
p 0.09
p 0.05
p 0.09
p 0.05
p 0.05
p 0.09
p 0.09
PD-1
FMT
NaCl
NaCl
E. H
Akk + E. H.
NaCl
NaCl
Akk
Akk + E. H.
All
NaCl
NaCl
Akk
Akk + E. H.
All
NaCl
B
F

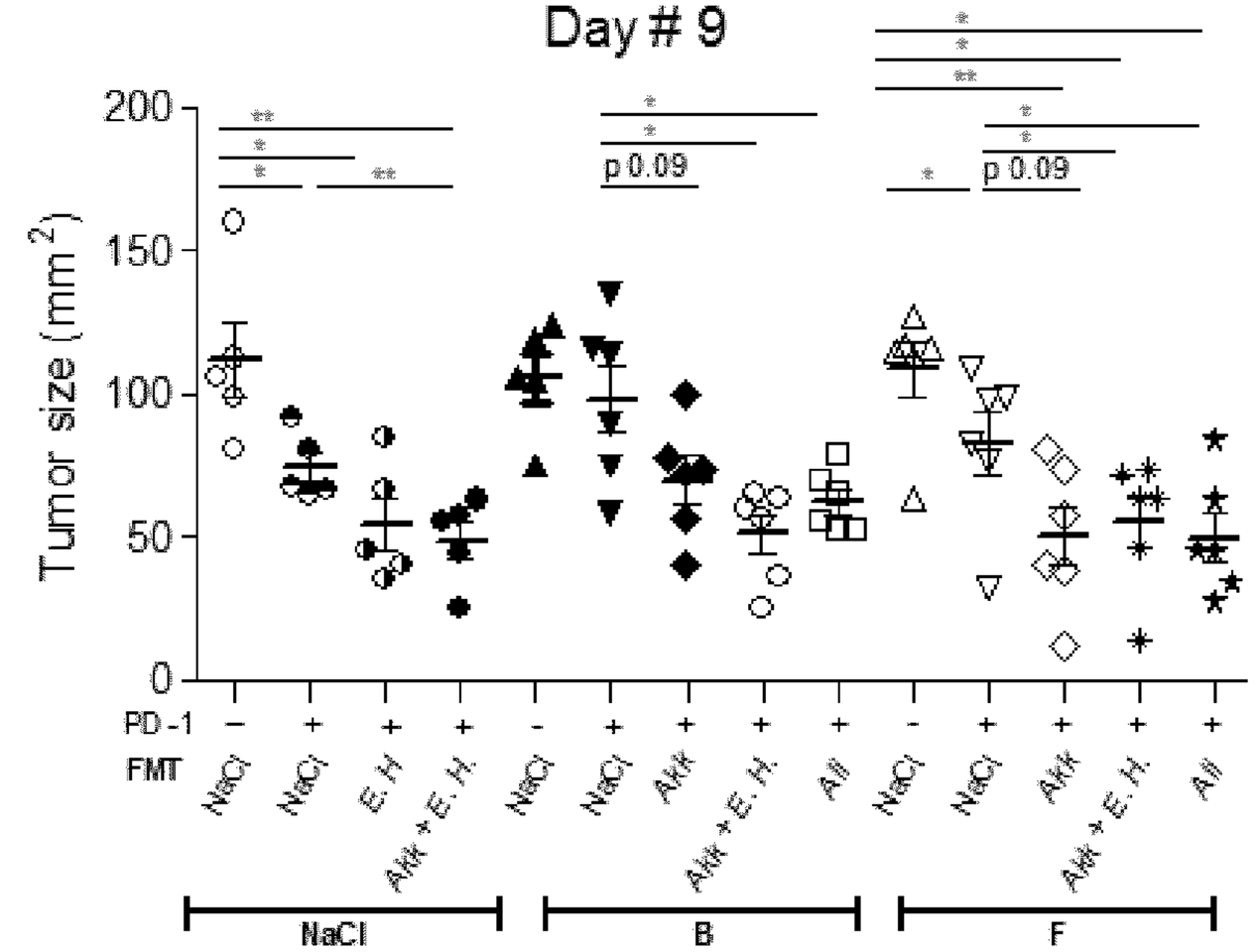

Day # 9
Tumor size (mm 2)
200
150
100
50
0
p 0.09
p 0.09
p 0.09
PD-1
FMT
NaCl
NaCl
E. H
Akk + E. H.
NaCl
NaCl
Akk
Akk + E. H.
All
NaCl
NaCl
Akk
Akk + E. H.
All
NaCl
B
F

Figure 17

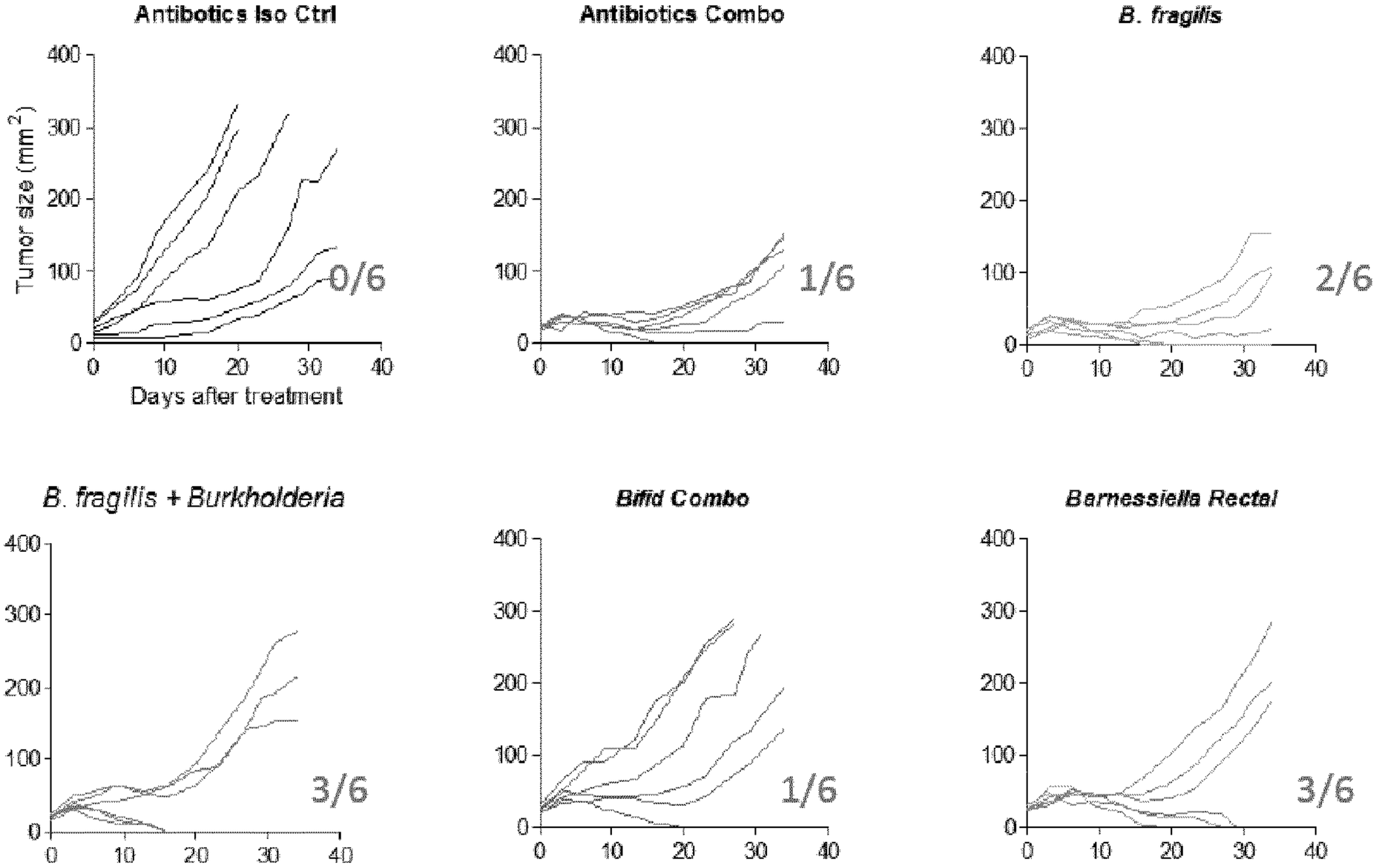


Figure 18

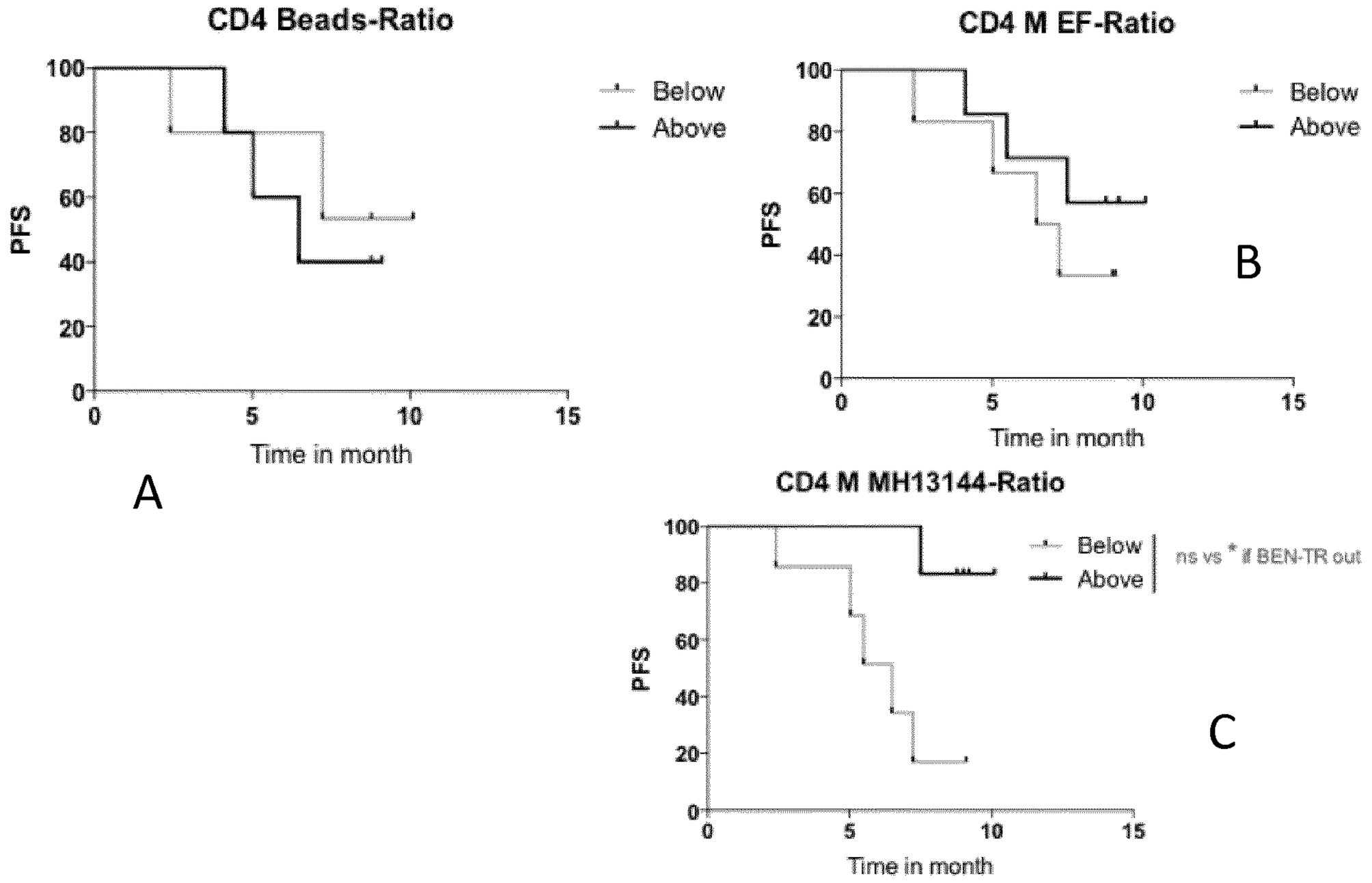
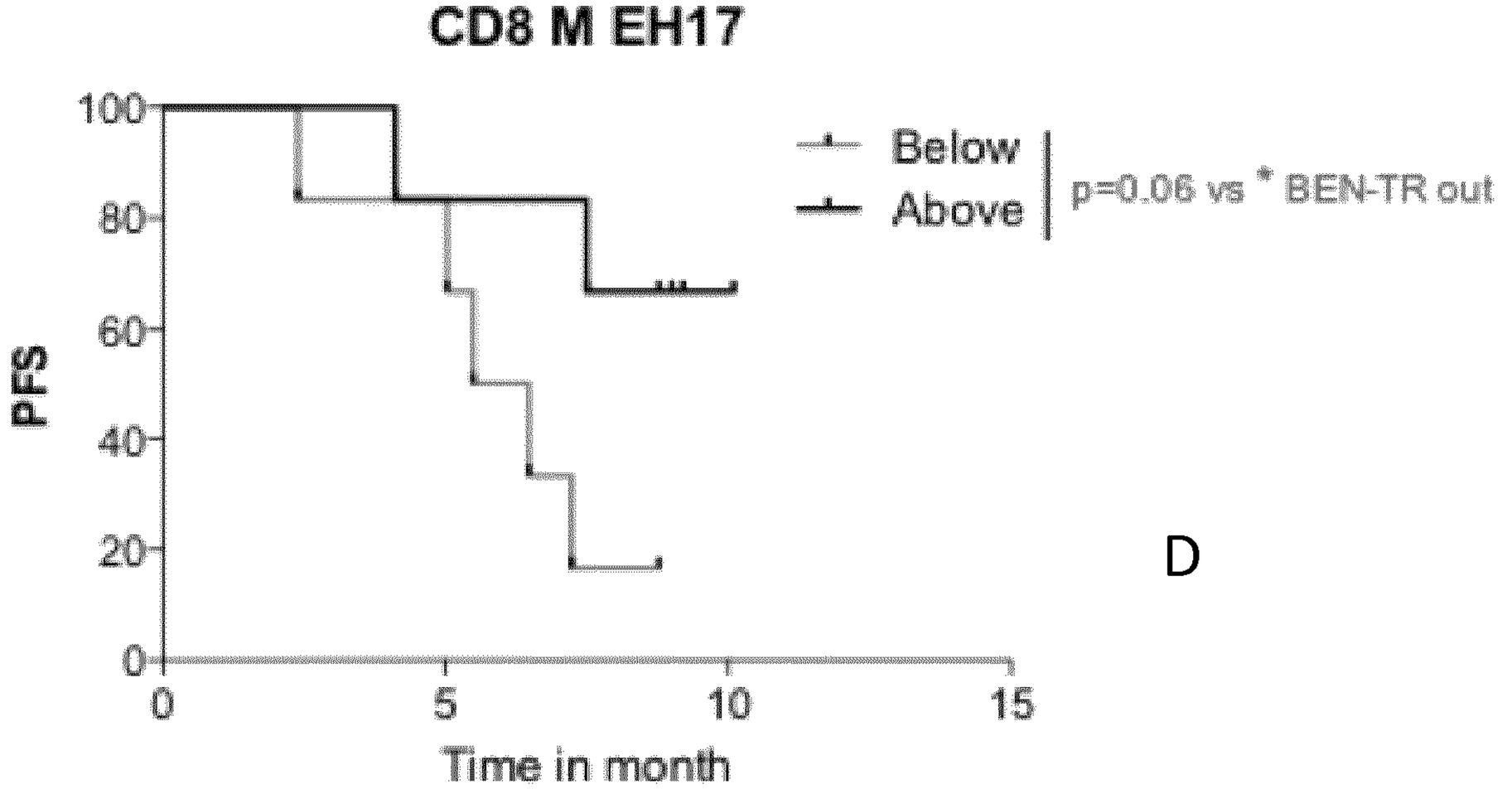
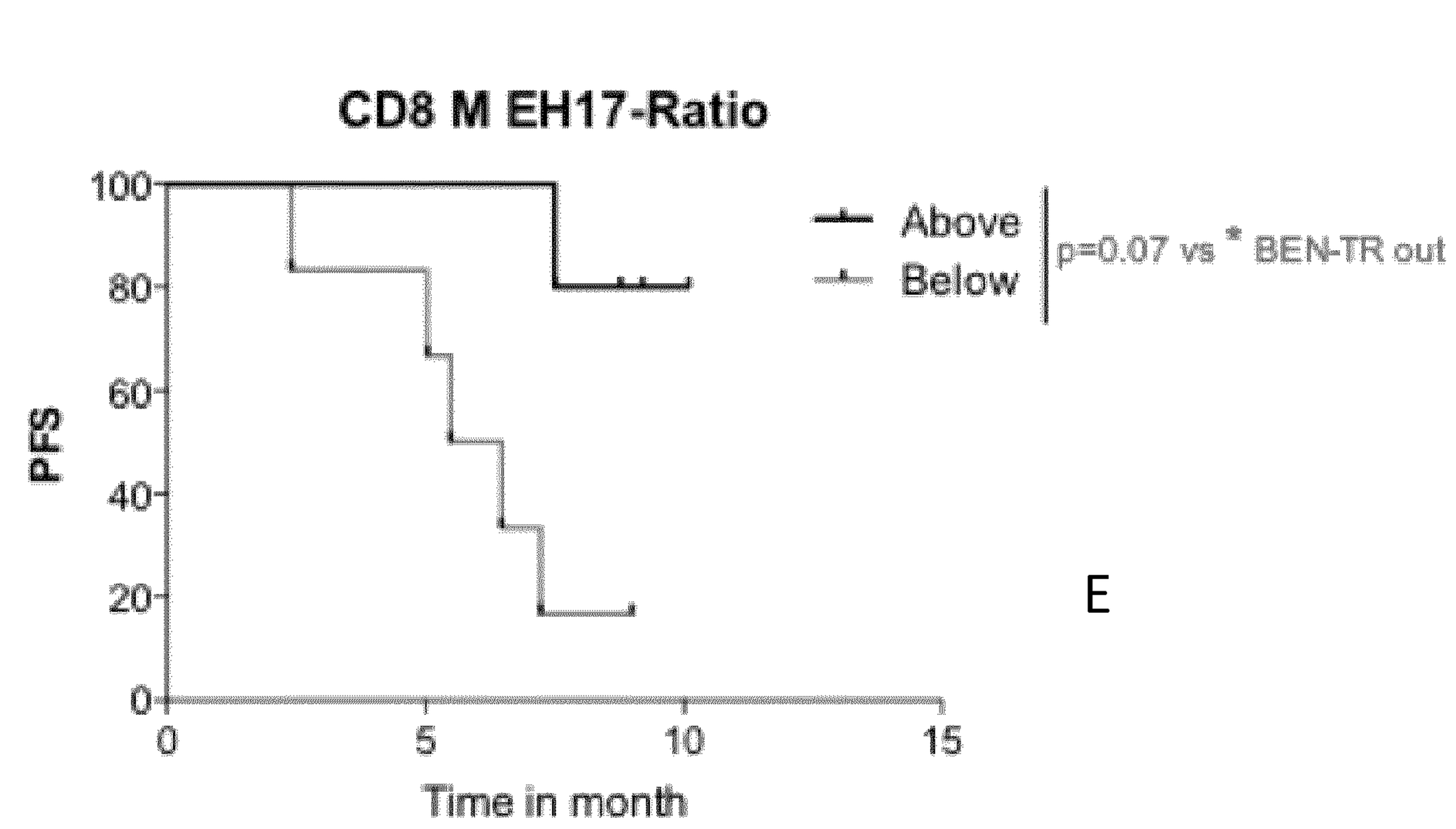


Figure 19 A-C

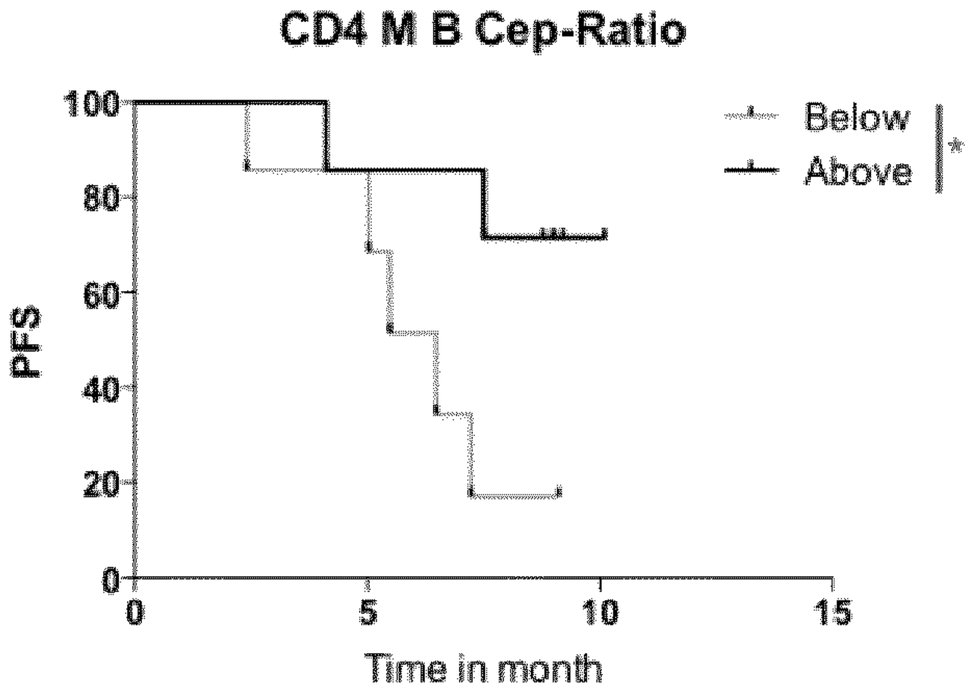


D

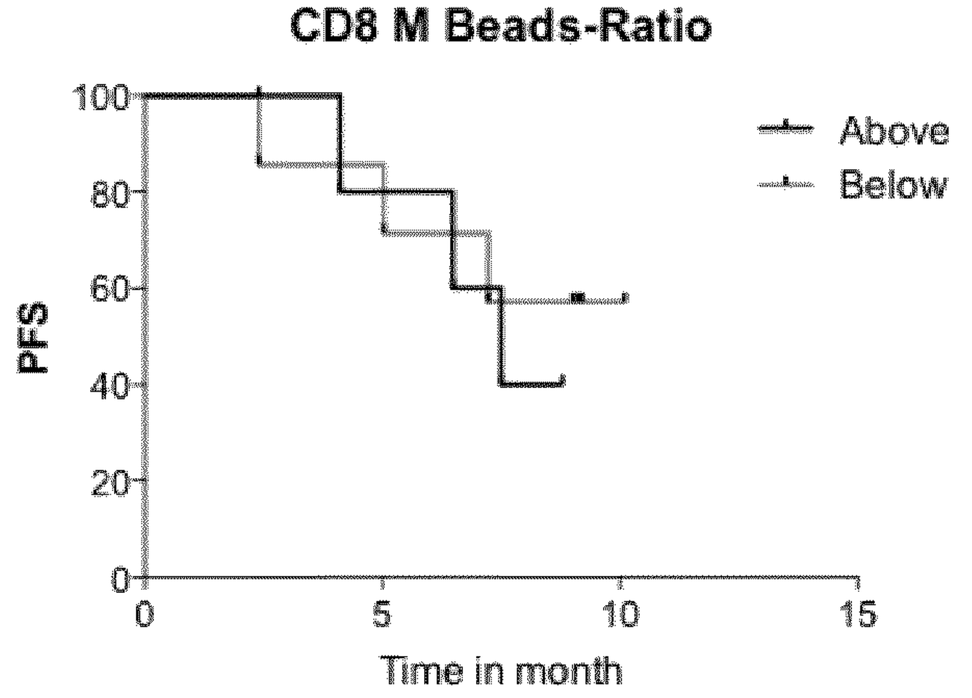


E

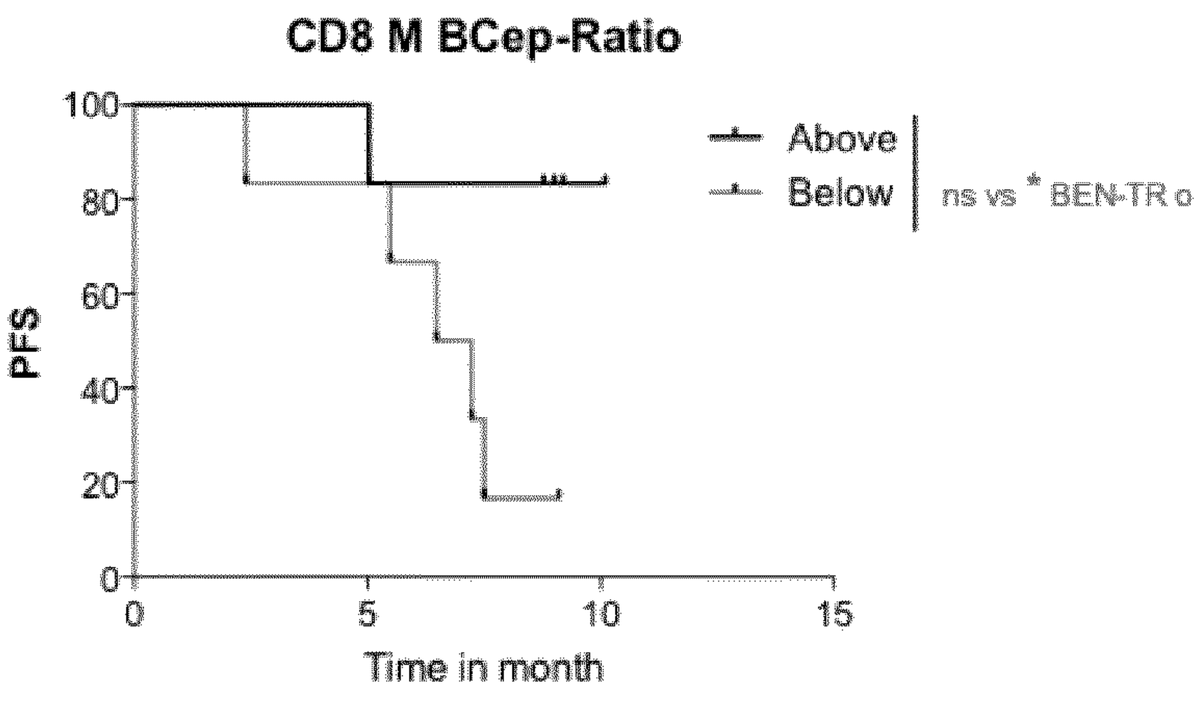
Figure 19 D-E



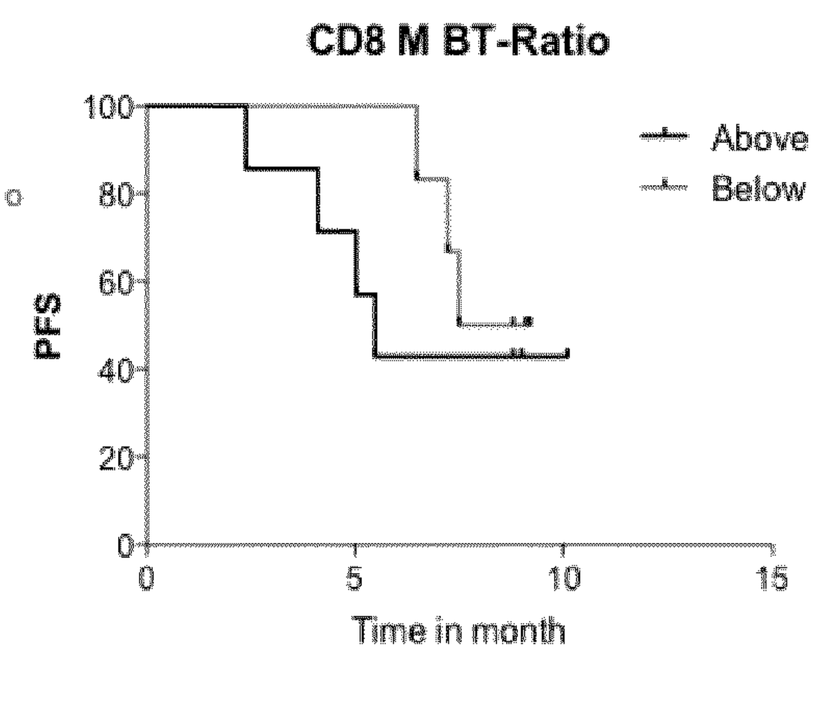
F



G

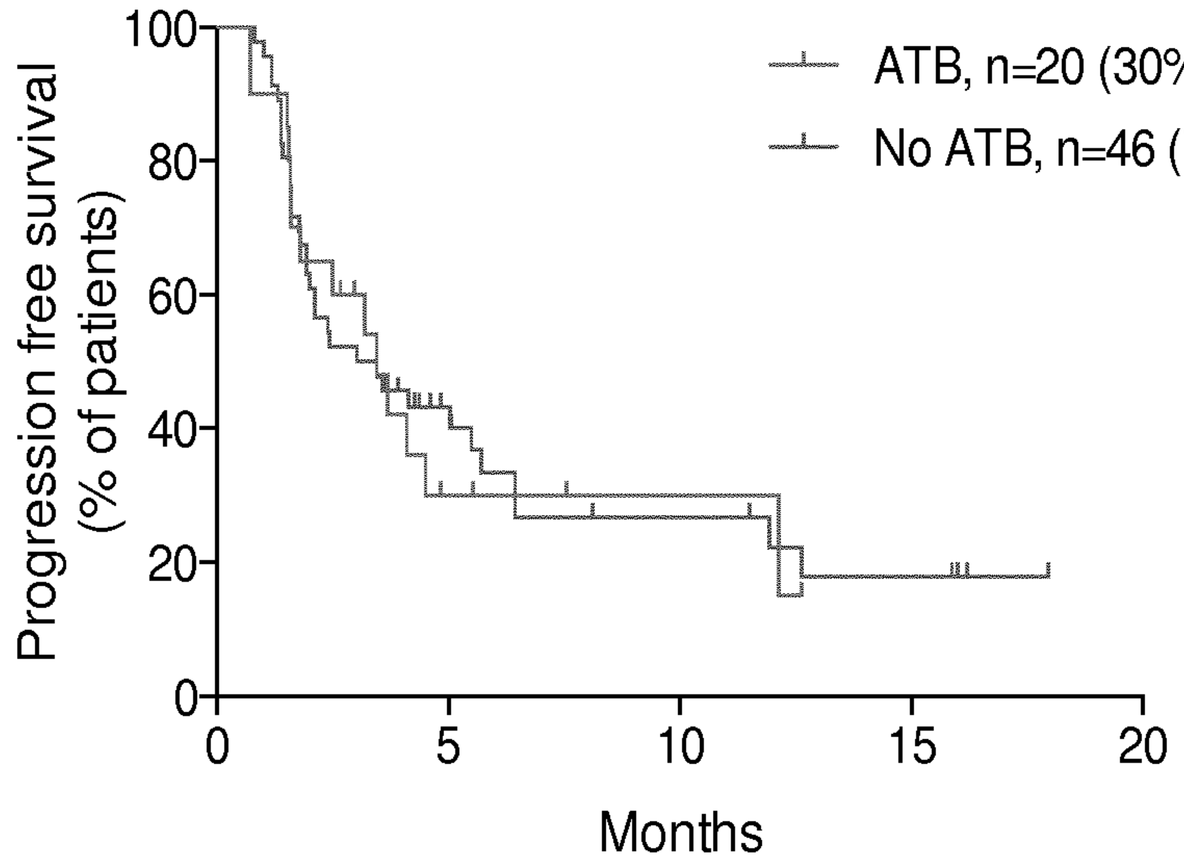


H



I

Figure 19 F-I


Progression free survival
(% of patients)
100
80
60
40
20
0
0
5
10
15
20
Months
ATB, n=20 (30%)
No ATB, n=46 (70%)

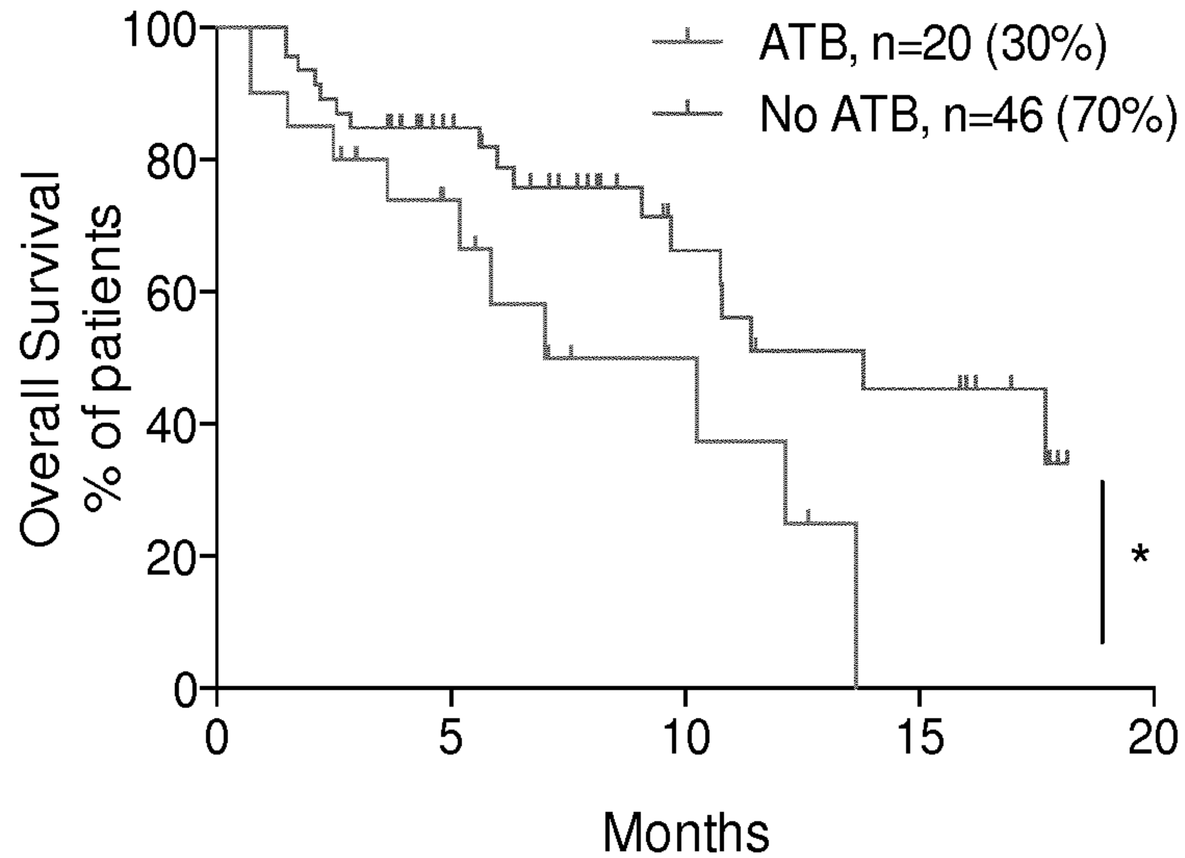
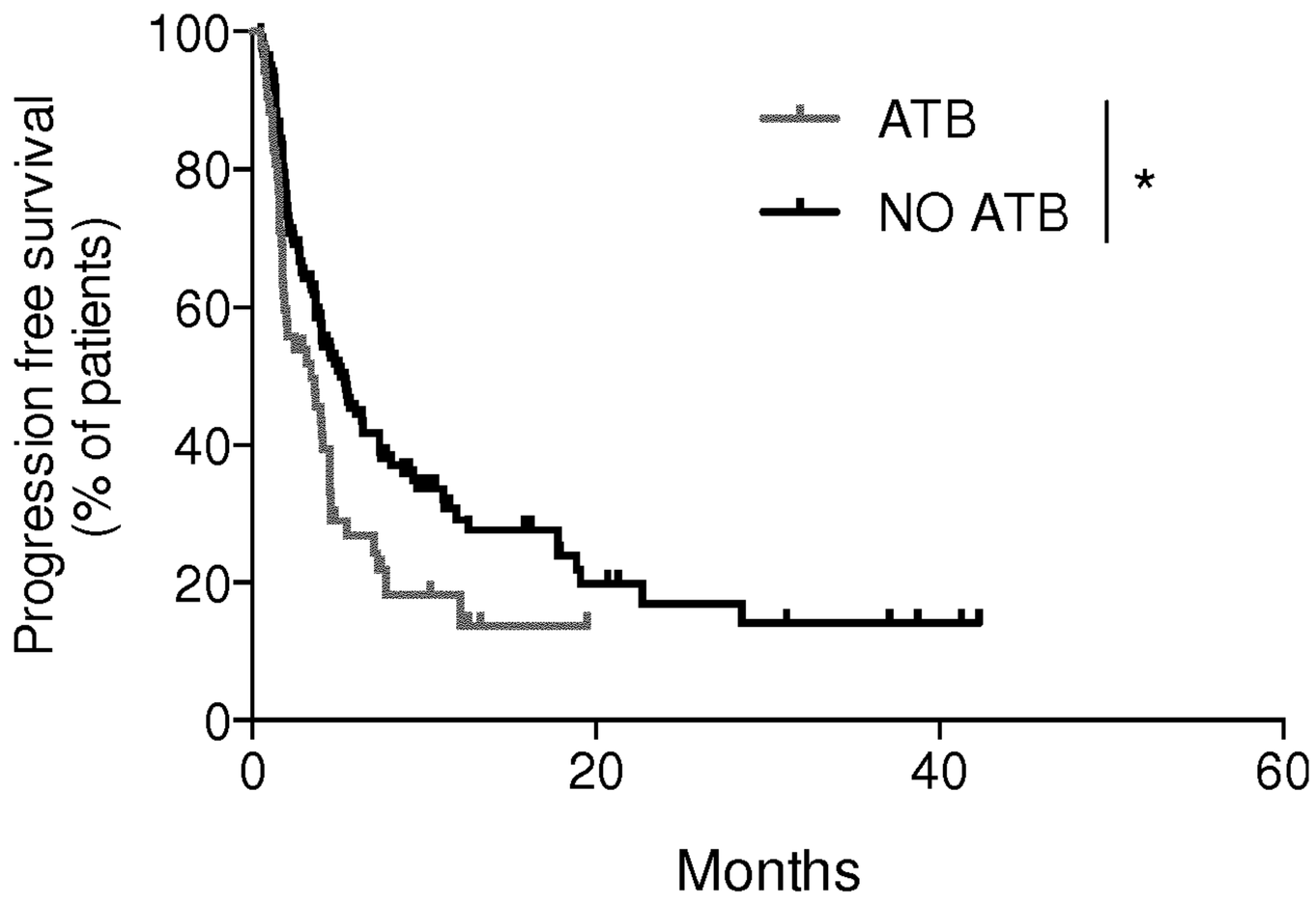

Overall Survival
% of patients
100
80
60
40
20
0
0
5
10
15
20
Months
ATB, n=20 (30%)
No ATB, n=46 (70%)
*

Figure 20


Progression free survival
(% of patients)
100
80
60
40
20
0
0
20
40
60
Months
ATB
NO ATB
*

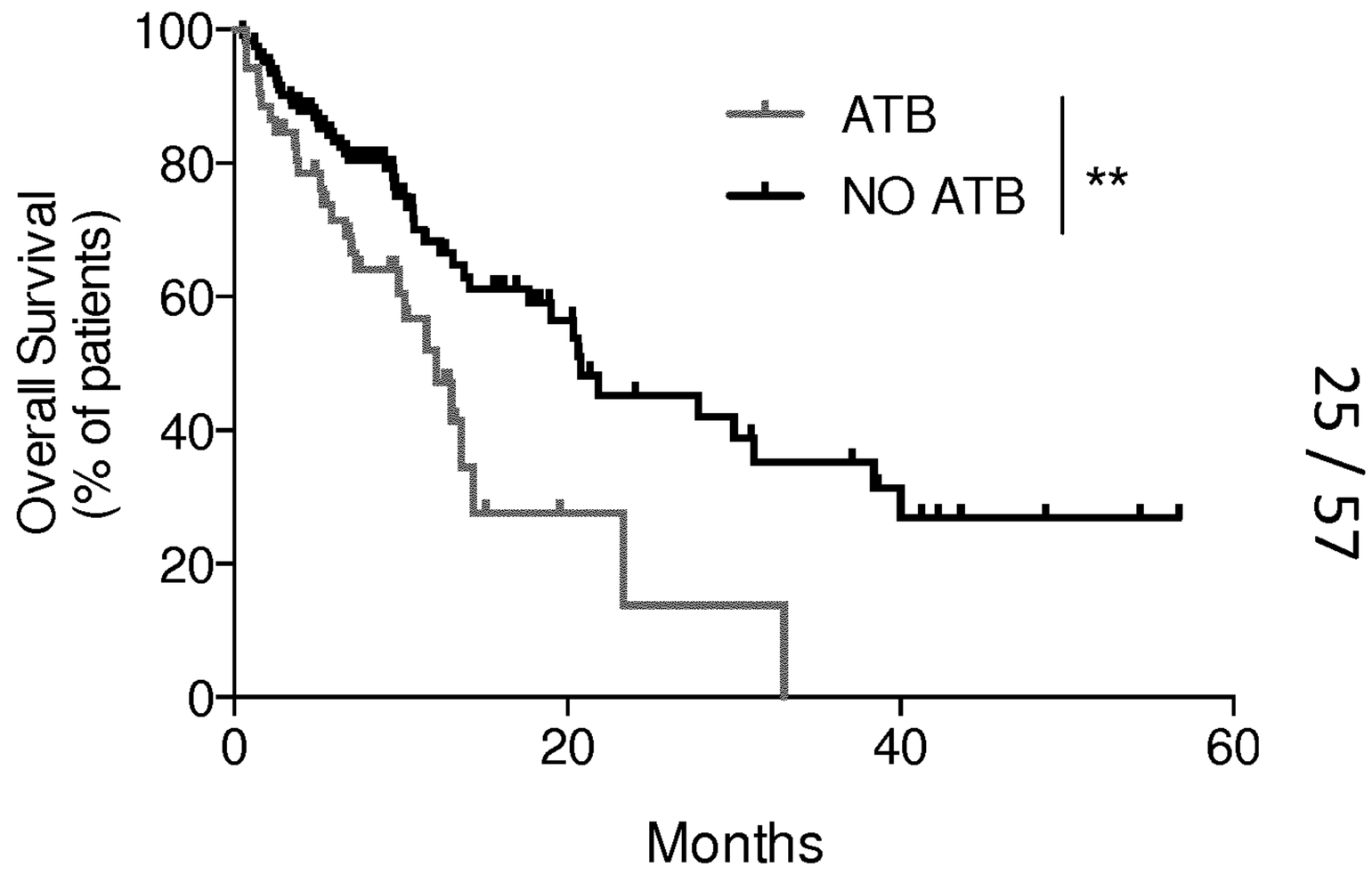

Overall Survival
(% of patients)
100
80
60
40
20
0
0
20
40
60
Months
ATB
NO ATB
**

Figure 21

18 MGS contrasted in at least 2 cohorts

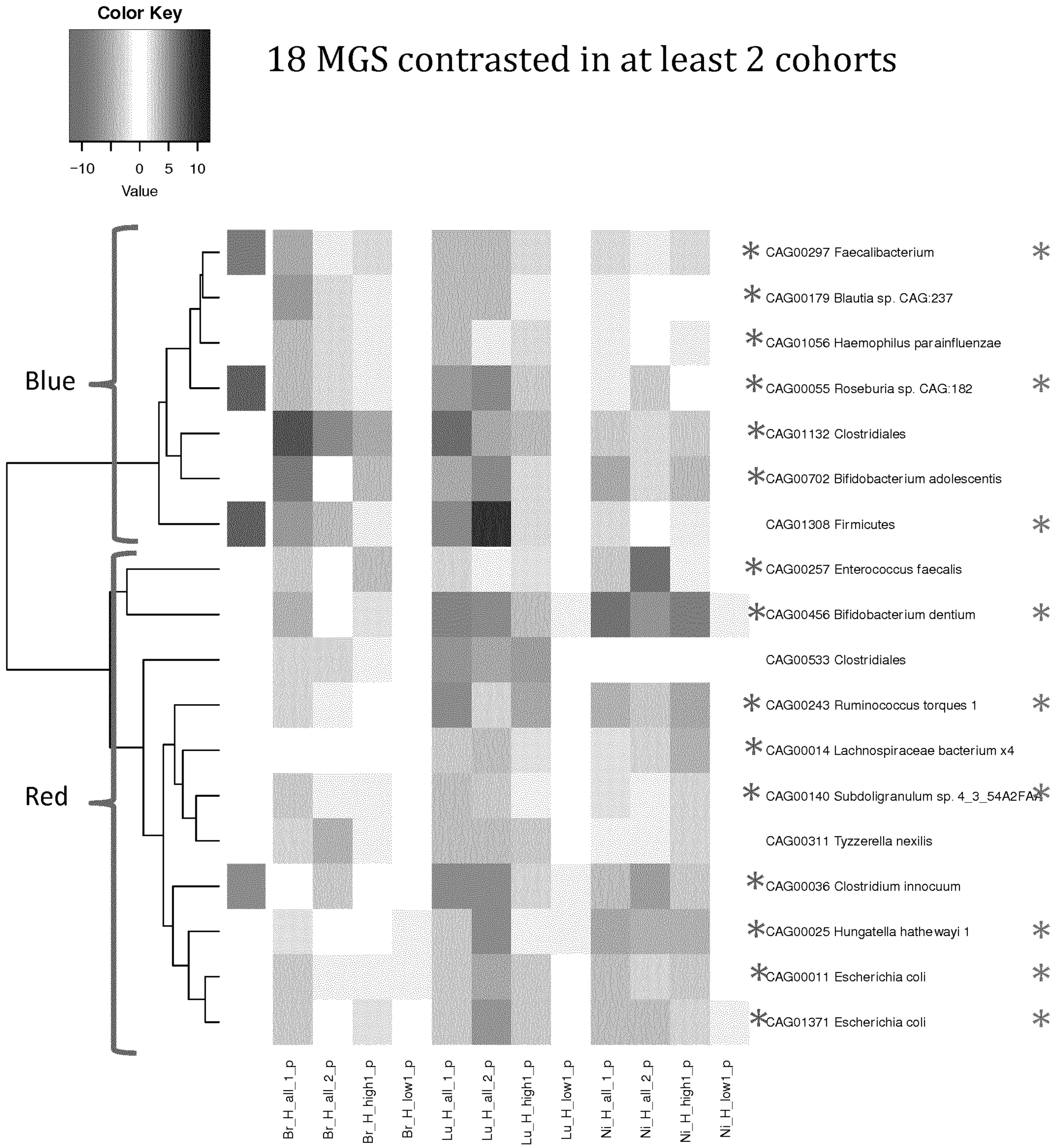


Figure 22

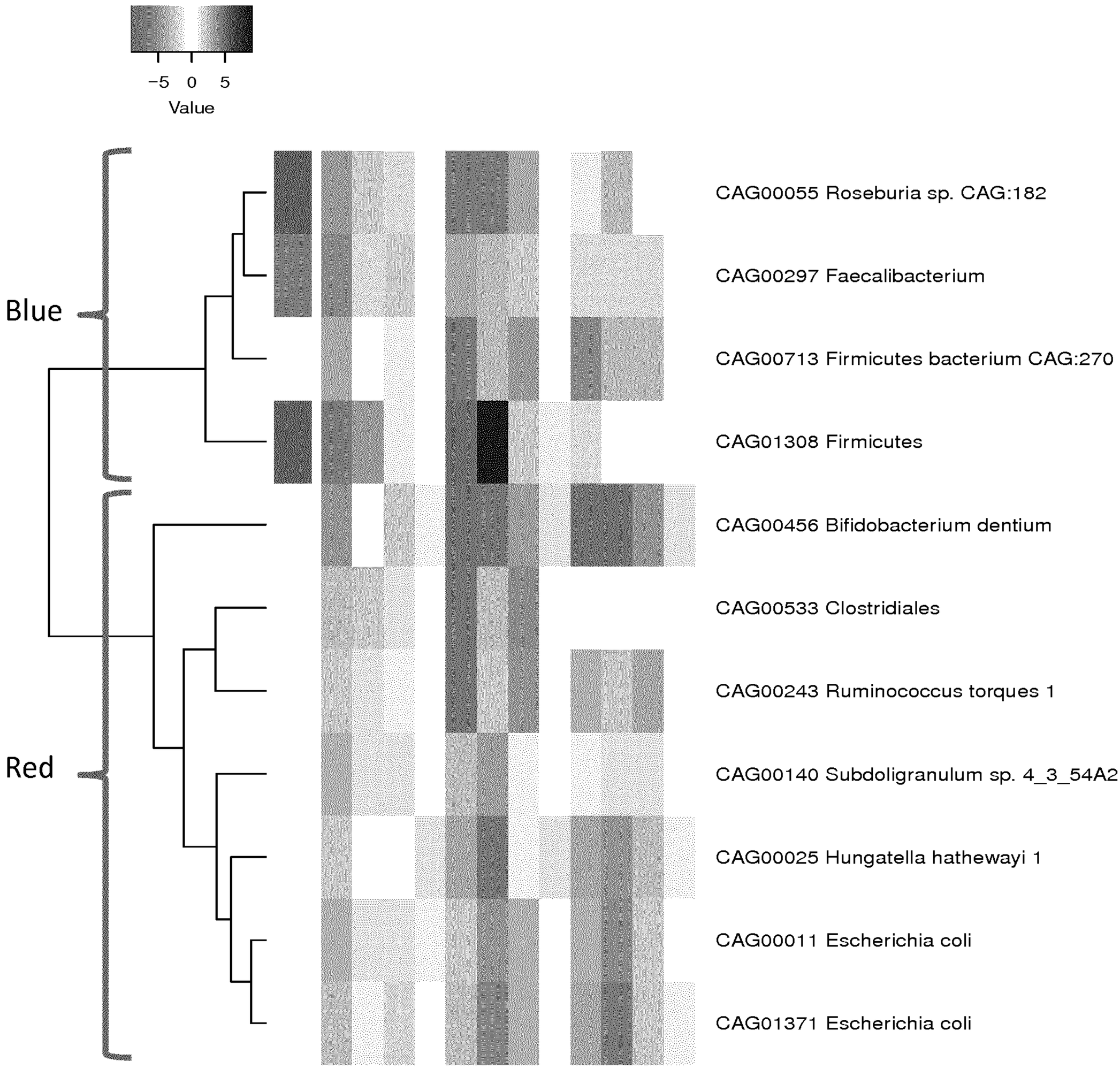

−5 0 5
Value
Blue
Red
CAG00055 Roseburia sp. CAG:182
CAG00297 Faecalibacterium
CAG00713 Firmicutes bacterium CAG:270
CAG01308 Firmicutes
CAG00456 Bifidobacterium dentium
CAG00533 Clostridiales
CAG00243 Ruminococcus torques 1
CAG00140 Subdoligranulum sp. 4_3_54A2FAA
CAG00025 Hungatella hathewayi 1
CAG00011 Escherichia coli
CAG01371 Escherichia coli
Br_H_all_1_p
Br_H_all_2_p
Br_H_high1_p
Br_H_low1_p
Lu_H_all_1_p
Lu_H_all_2_p
Lu_H_high1_p
Lu_H_low1_p
Ni_H_all_1_p
Ni_H_all_2_p
Ni_H_high1_p
Ni_H_low1_p

Figure 23

TTP6 V1-V2

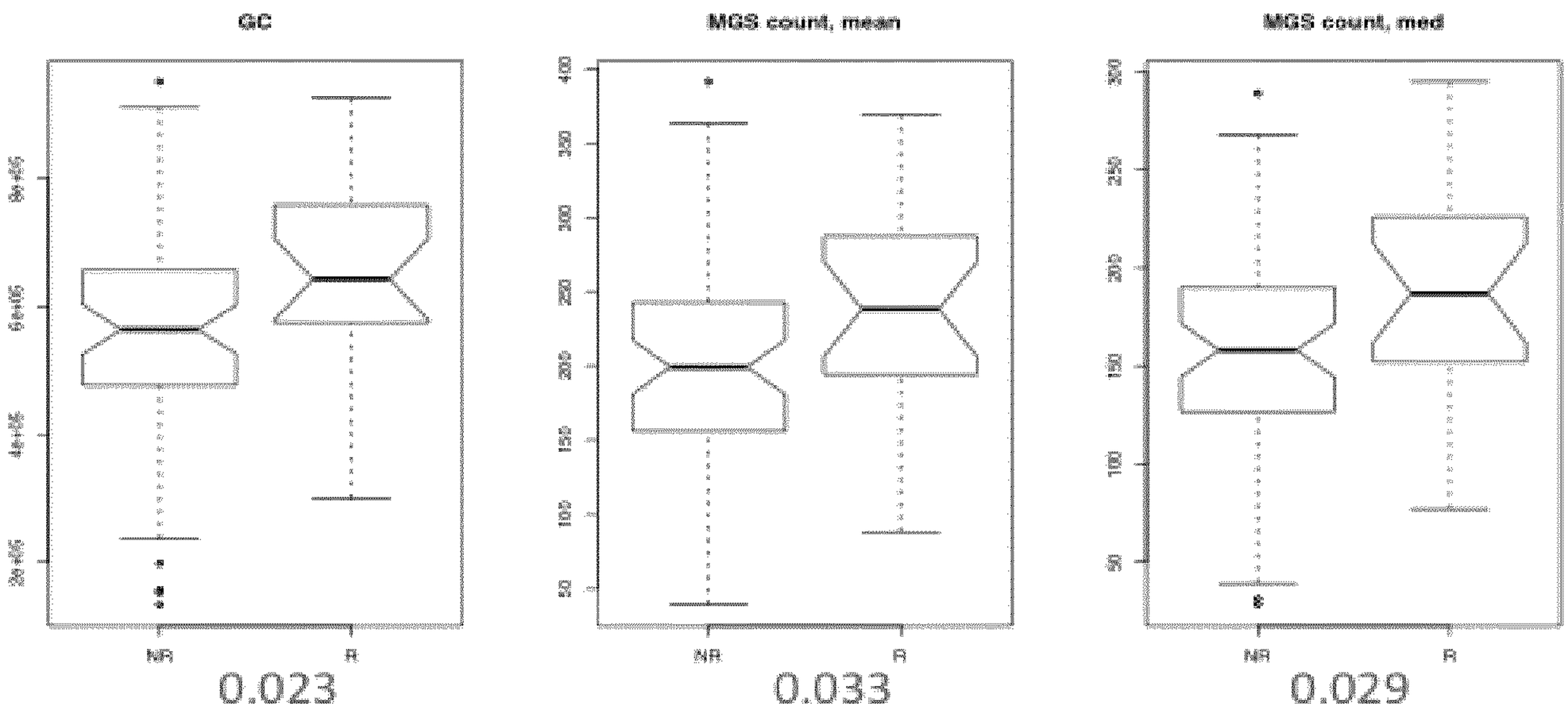
no_AB

1 SIGNAL ?

71 MGS

no species common Lu and Ni

1 species common batch 1 et 2*



higher richness for responders

	NR		R	
	Lu41	Ni21	Lu12	Ni14
batch1	17-1	7	8-1	6-1
batch2	20	12	1	8

Figure 24

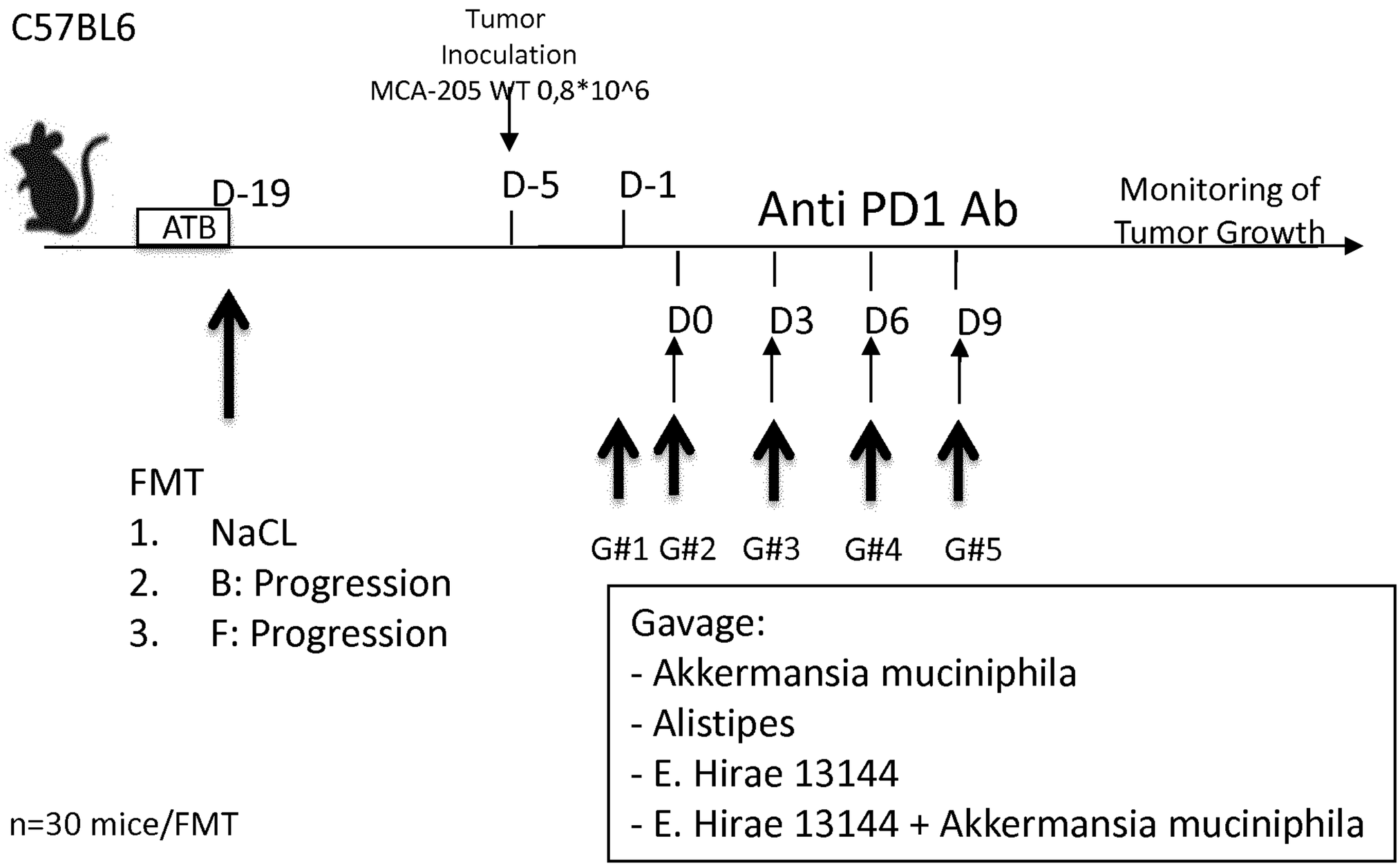


Figure 25

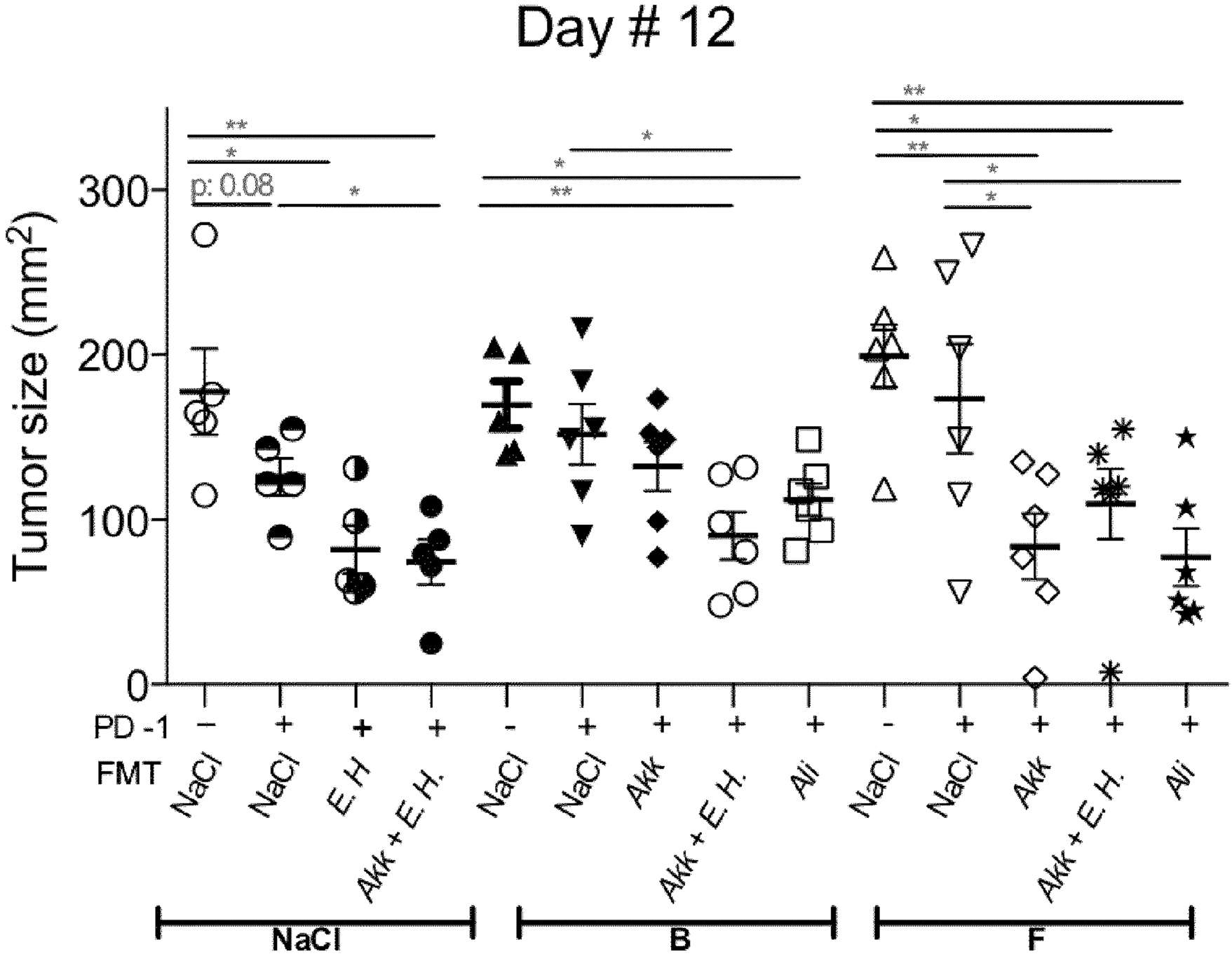


Figure 26

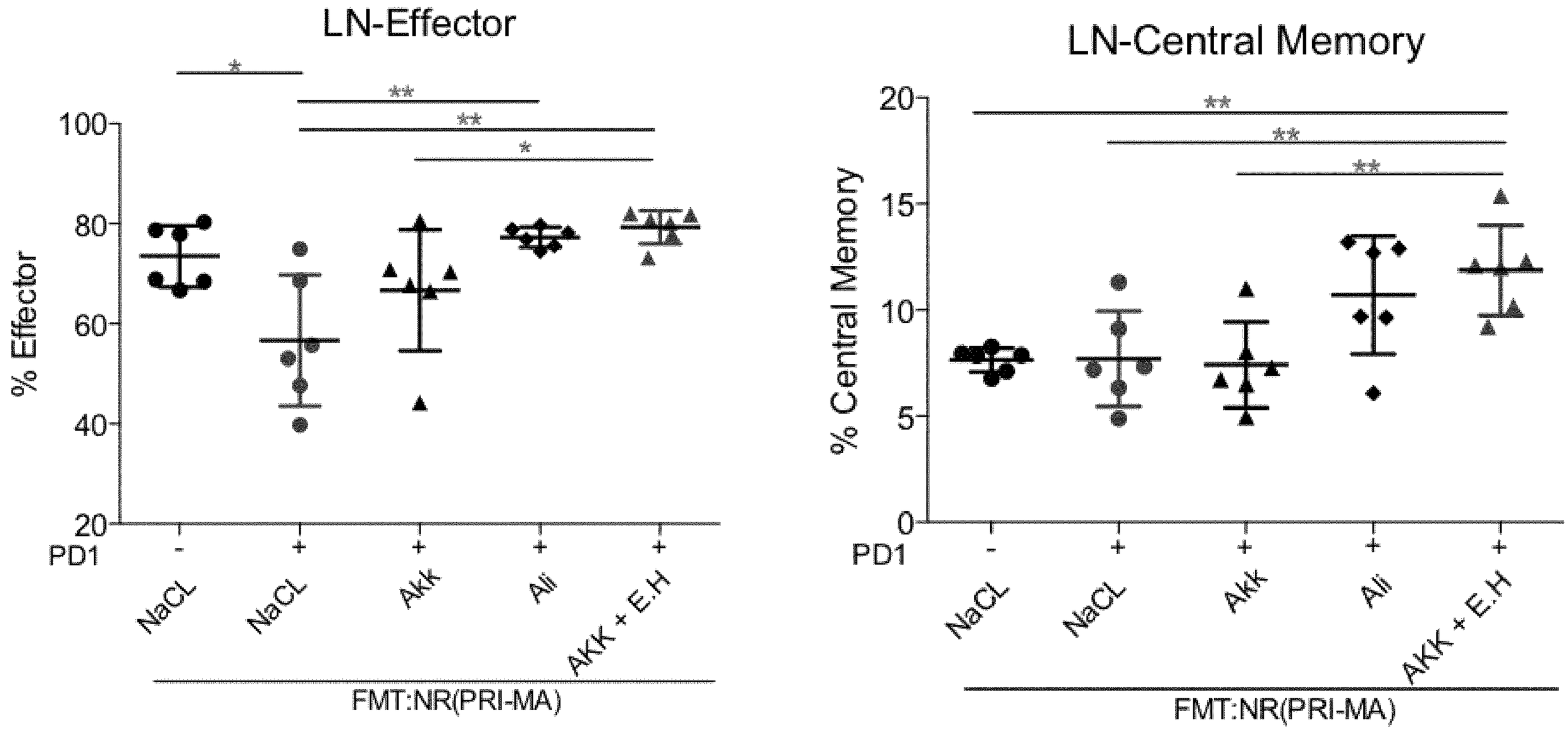
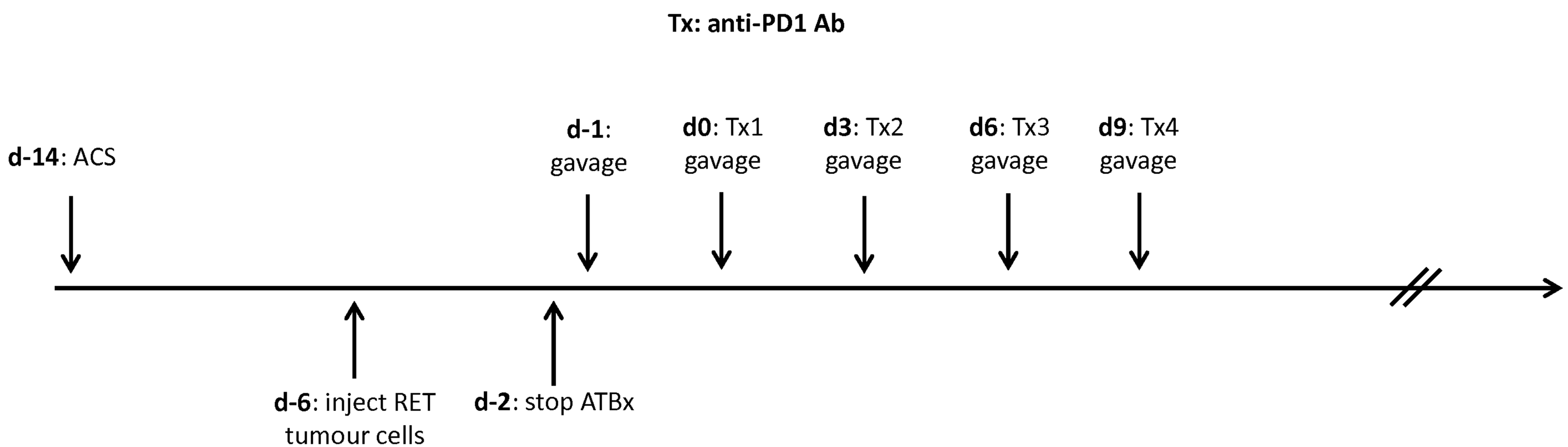

LN-Effector
% Effector
100
80
60
40
20
*
**
**
*
PD1
-
+
+
+
+
NaCL
NaCL
Akk
Ali
AKK + E.H
FMT:NR(PRI-MA)
LN-Central Memory
% Central Memory
20
15
10
5
0
**
**
**
PD1
-
+
+
+
+
NaCL
NaCL
Akk
Ali
AKK + E.H
FMT:NR(PRI-MA)

Figure 27



	d-1	d0	d3	d6	d9
6.aPD1+ natural recolonisation (3 days)+ 3x Akk	Natural recolonisation	aPD1+ Natural recolonisation	aPD1+ Akkermansia	aPD1+ Akkermansia	aPD1+ Akkermansia
7. aPD1+ 2x EH13144 + 3x Akk	EH13144	aPD1+ EH13144	aPD1+ Akkermansia	aPD1+ Akkermansia	aPD1+ Akkermansia
8. aPD1+ 2x Tenue + 3x Akk	Tenue	aPD1+Tenue	aPD1+ Akkermansia	aPD1+ Akkermansia	aPD1+ Akkermansia
9. aPD1 + 5x Alistipes	Alistipes	aPD1+Alistipes	aPD1+Alistipes	aPD1+Alistipes	aPD1+Alistipes

Figure 28

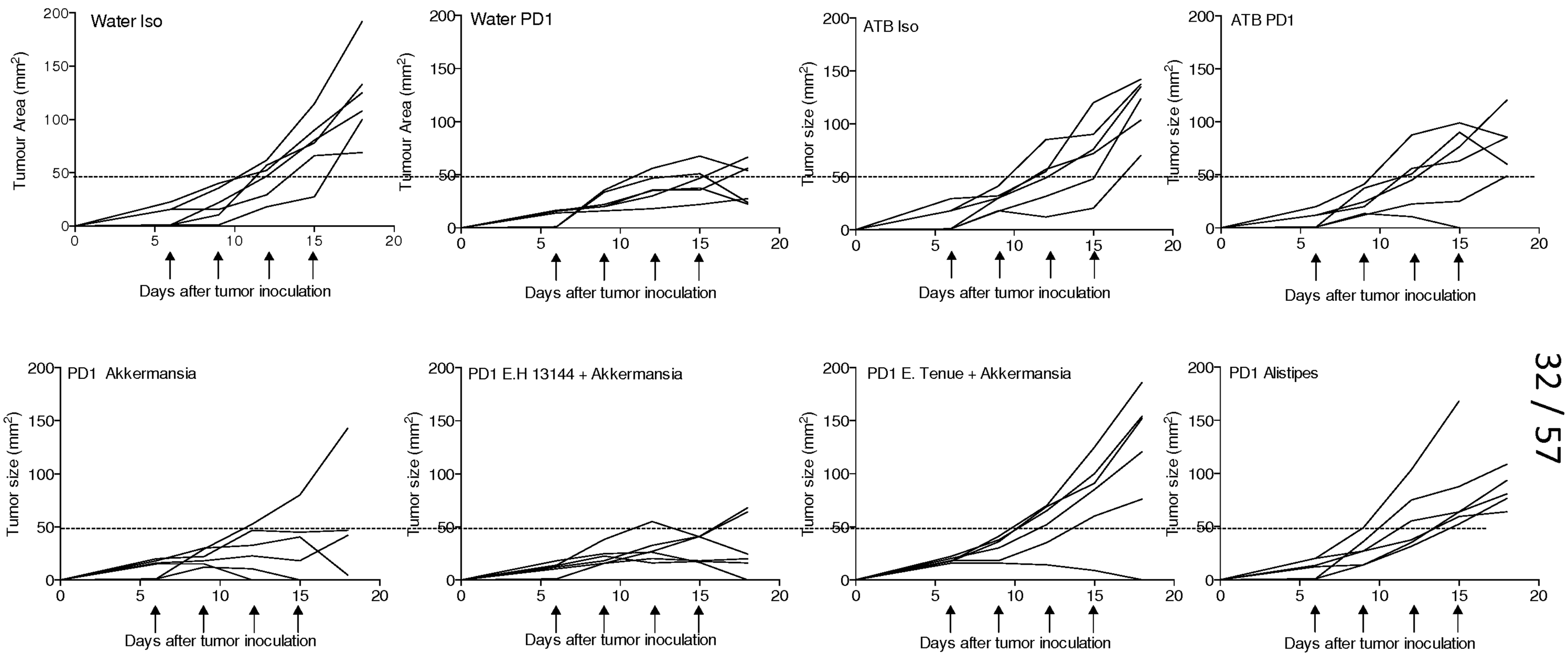

Water Iso
Water PD1
ATB Iso
ATB PD1
PD1 Akkermansia
PD1 E.H 13144 + Akkermansia
PD1 E. Tenue + Akkermansia
PD1 Alistipes
Tumour Area (mm2)
Tumor size (mm2)
Days after tumor inoculation
0
5
10
15
20
50
100
150
200

Figure 29

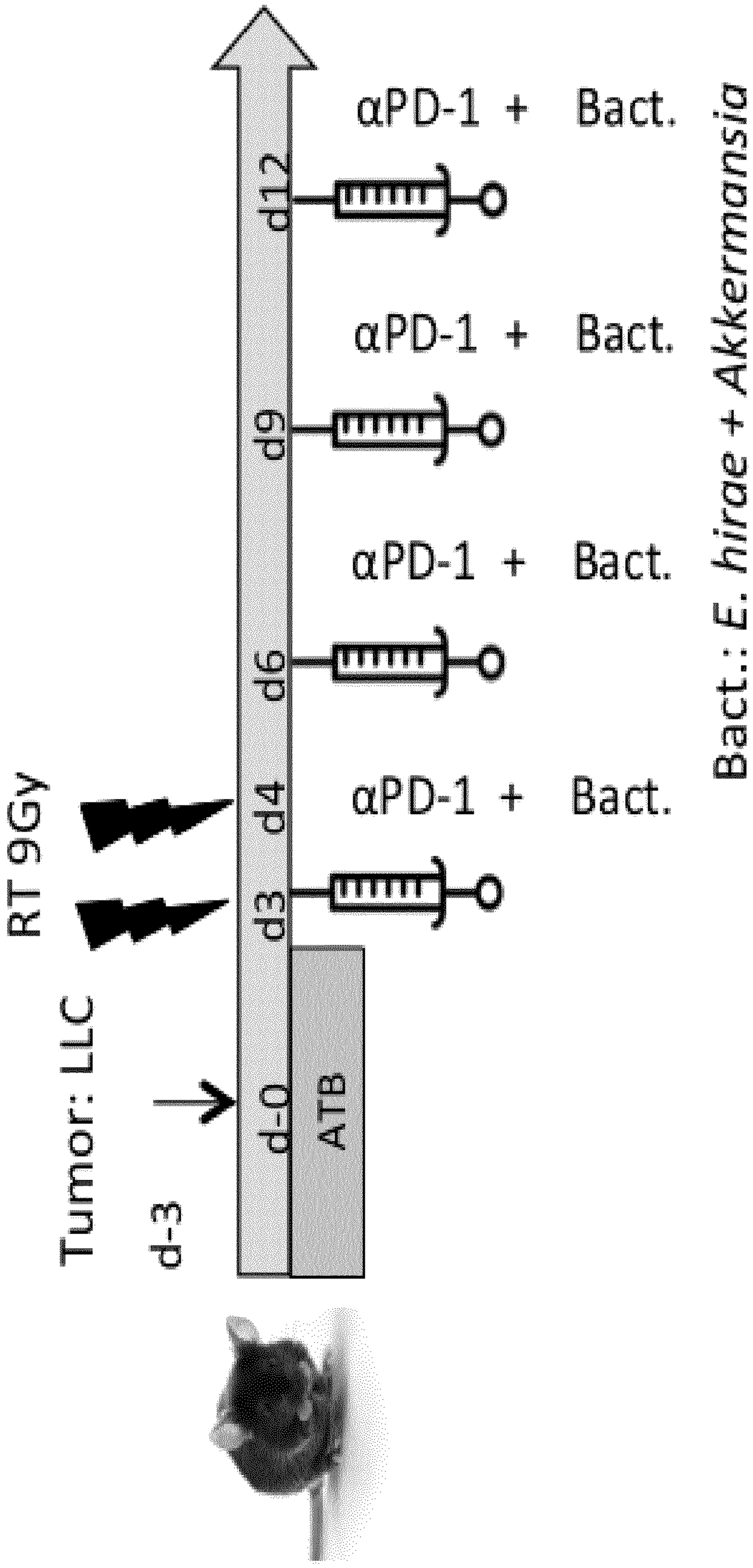

Tumor: LLC
RT 9Gy
d-3
d-0
ATB
d3
d4
αPD-1 + Bact.
d6
αPD-1 + Bact.
d9
αPD-1 + Bact.
d12
αPD-1 + Bact.
Bact.: E. hirae + Akkermansia muciniphila

Figure 30

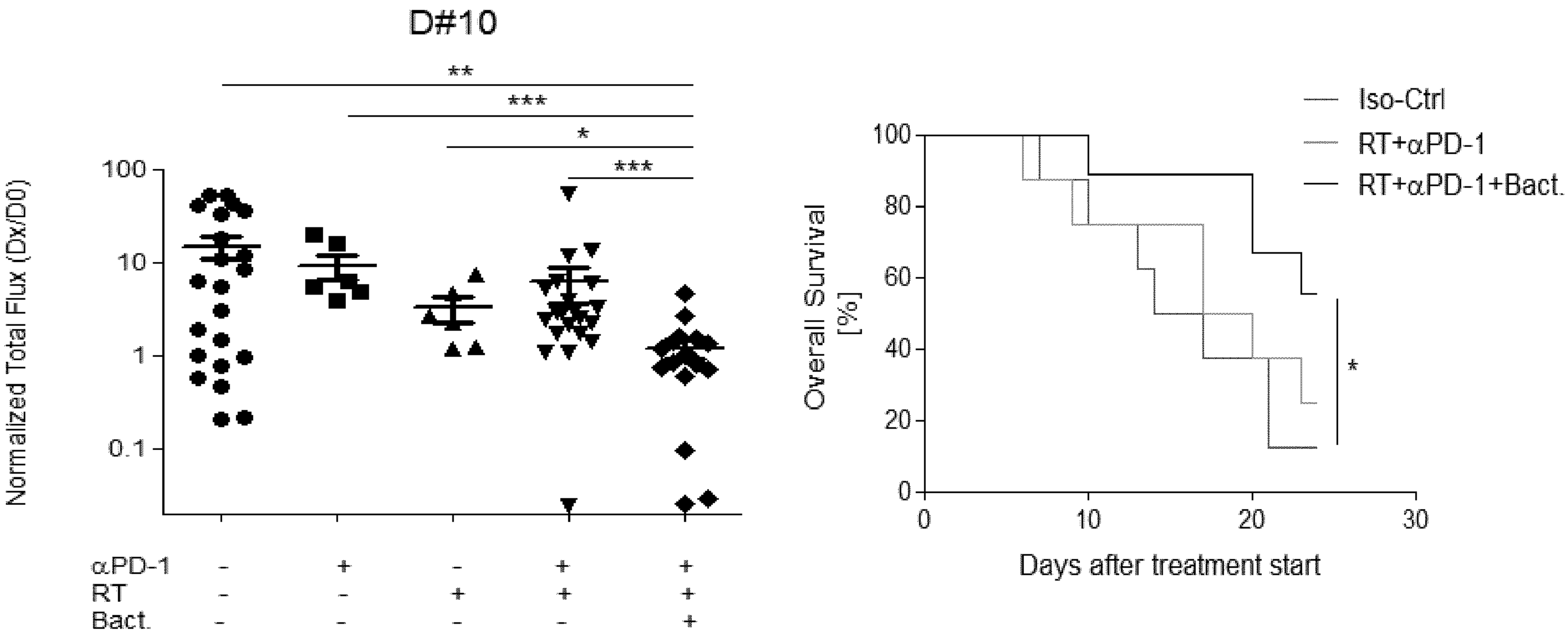
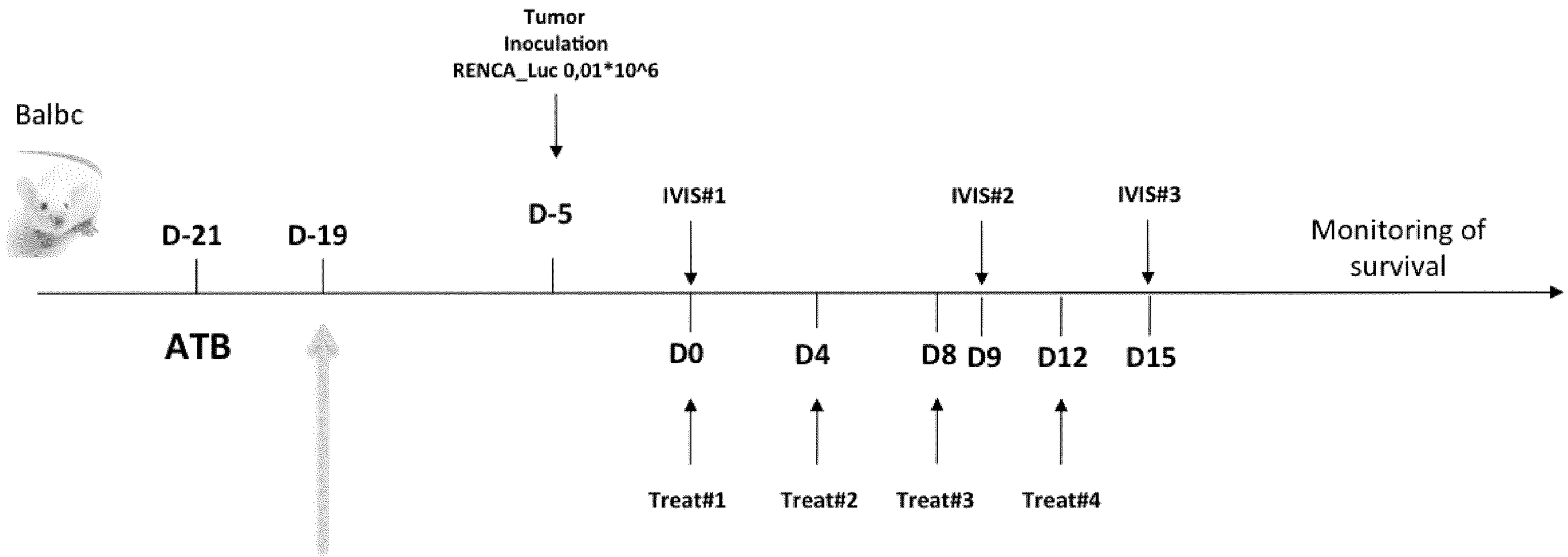

D#10
**
***
*
***
Normalized Total Flux (Dx/D0)
100
10
1
0.1
αPD-1 - + - + +
RT - - + + +
Bact. - - - - +
Iso-Ctrl
RT+αPD-1
RT+αPD-1+Bact.
Overall Survival [%]
100
80
60
40
20
0
0
10
20
30
Days after treatment start
*

Figure 31



Patients	Outcome	Akkermansia muciniphila CAG00301	Blautia CAG00112	Bacteroides nordii CAG00116	Blautia CAG00179	Ruminococcus Torque CAG00243	Ruminococcus CAG00250	Eubacterium CAG00469	Alistipes species CAG00510	Alistipes species CAG00646	Ruminococcus Bacterium CAG00949	Ruminococcus Torque CAG01262
B	Non responder	0	8,68E-07	0	0	5,39E-07	0	8,98E-07	0	0	0	0
C	Non responder	0	4,68E-07	1,30E-07	0	2,66E-07	0	2,38E-07	0	0	0	0
D	Responder	1,71E-06	6,58E-08	5,30E-09	0	6,54E-08	0	2,45E-08	0	0	1,89E-08	0
	Cut-off value	0,01598361	NA	1,22E-05	2,03E+01	0.0004426992	NA	4,82E-05	0,017485	0,001840316	NA	NA

Figure 32

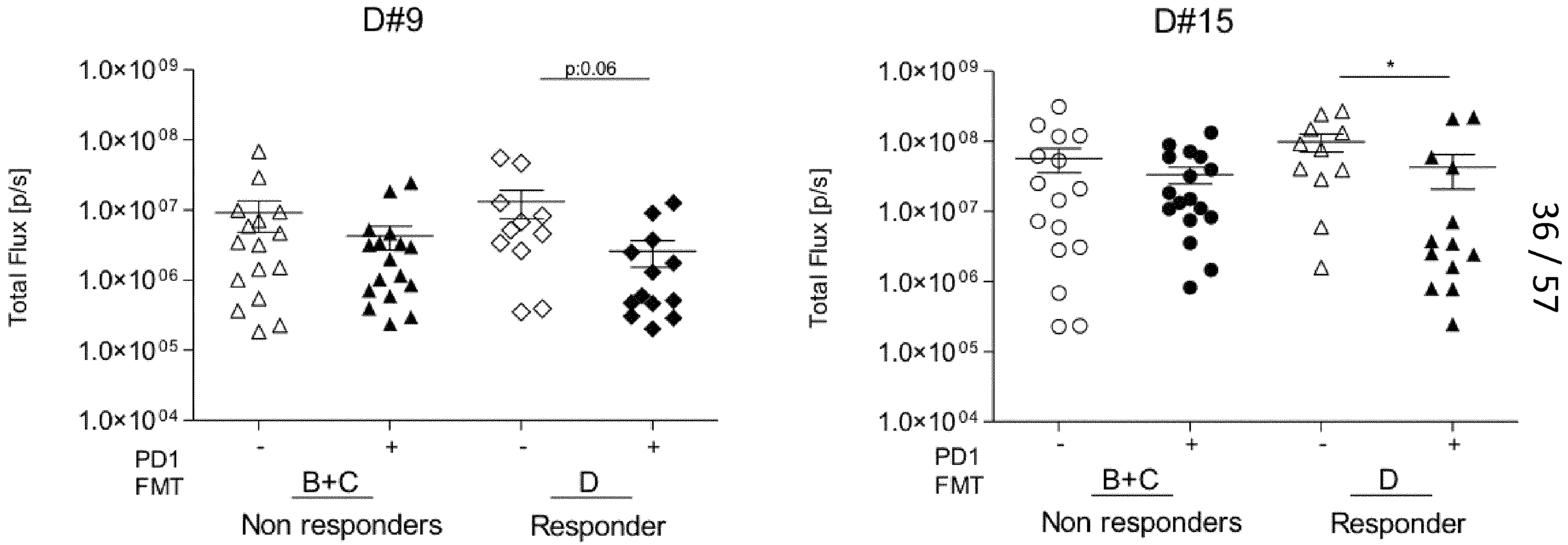

D#9
p:0.06
1.0×10^09
1.0×10^08
1.0×10^07
1.0×10^06
1.0×10^05
1.0×10^04
Total Flux [p/s]
PD1
FMT
-
+
-
+
B+C
D
Non responders
Responder
D#15
*
1.0×10^09
1.0×10^08
1.0×10^07
1.0×10^06
1.0×10^05
1.0×10^04
Total Flux [p/s]
PD1
FMT
-
+
-
+
B+C
D
Non responders
Responder

Figure 33

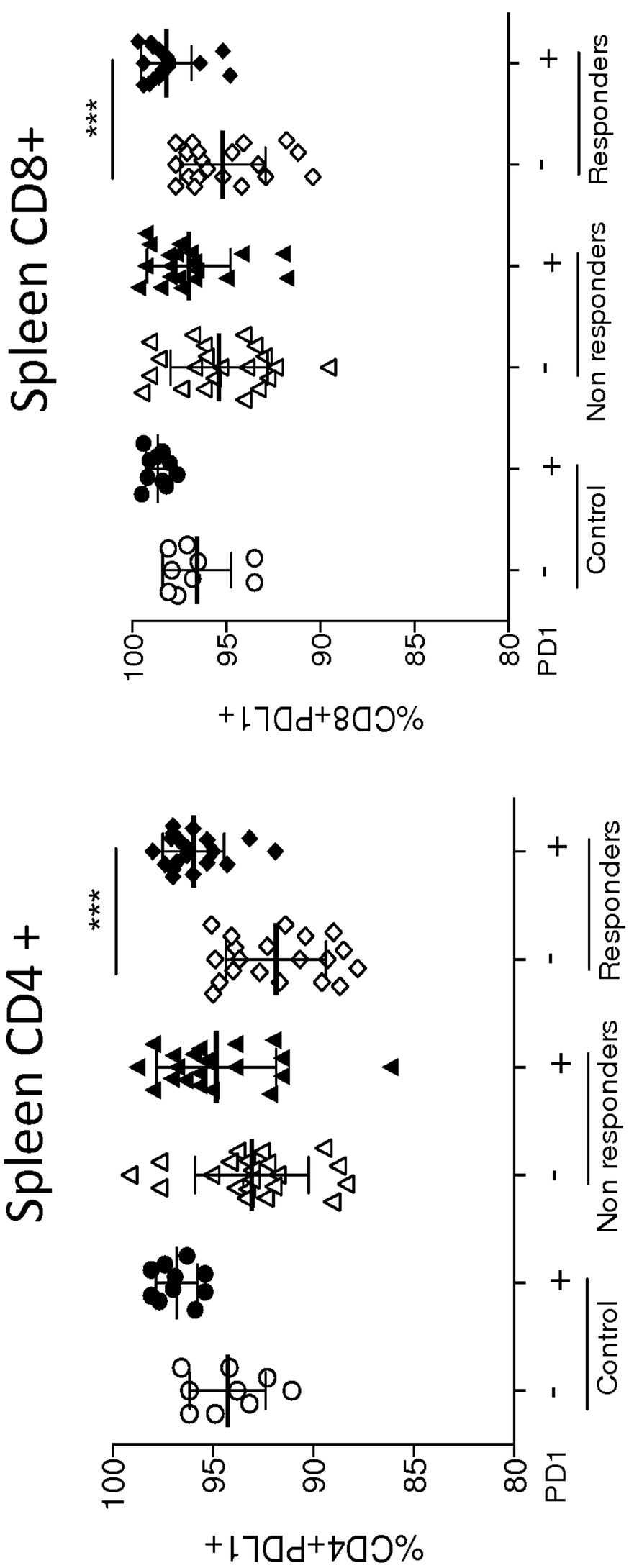
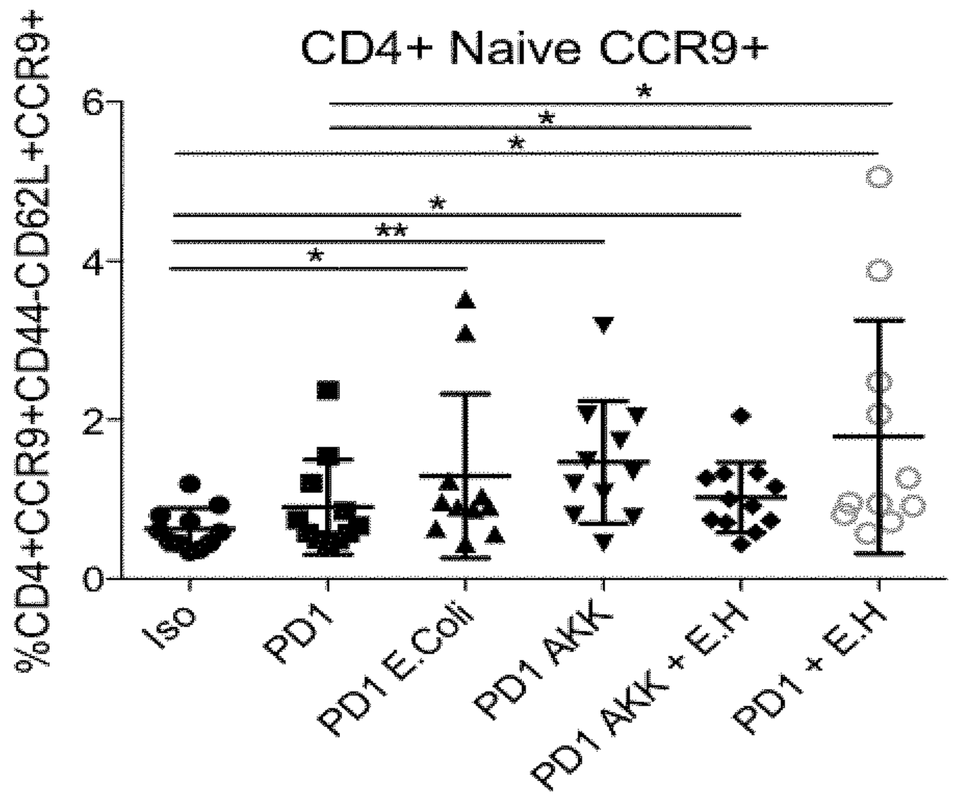


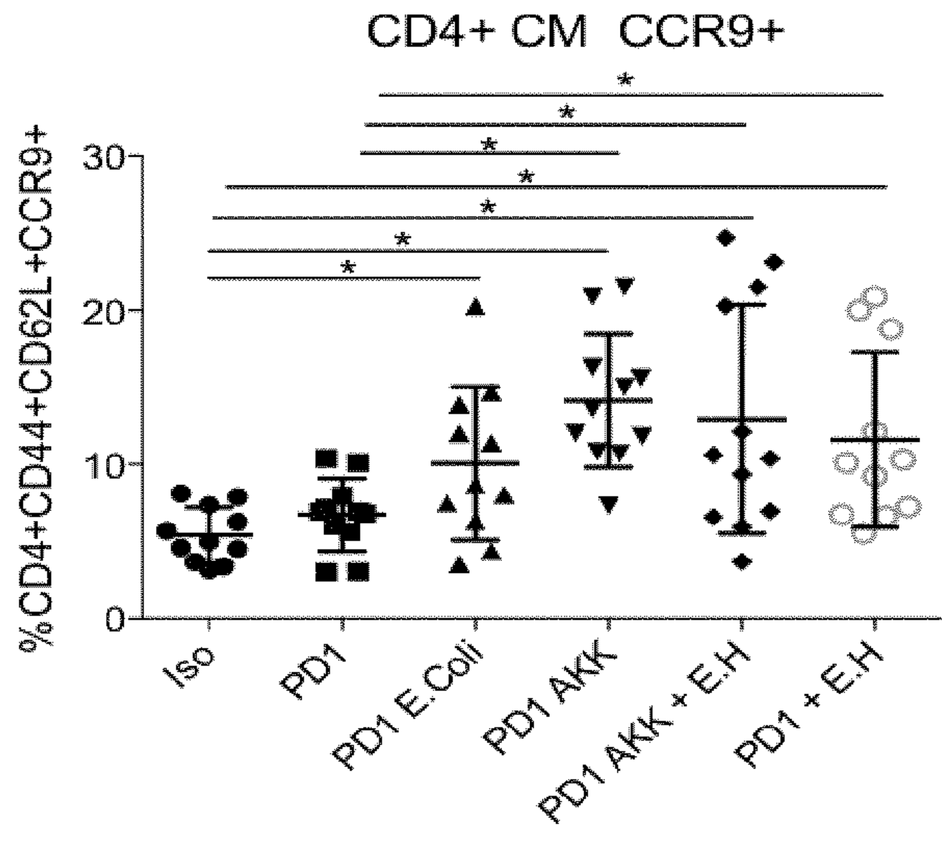
Figure 3

A. Post FMT

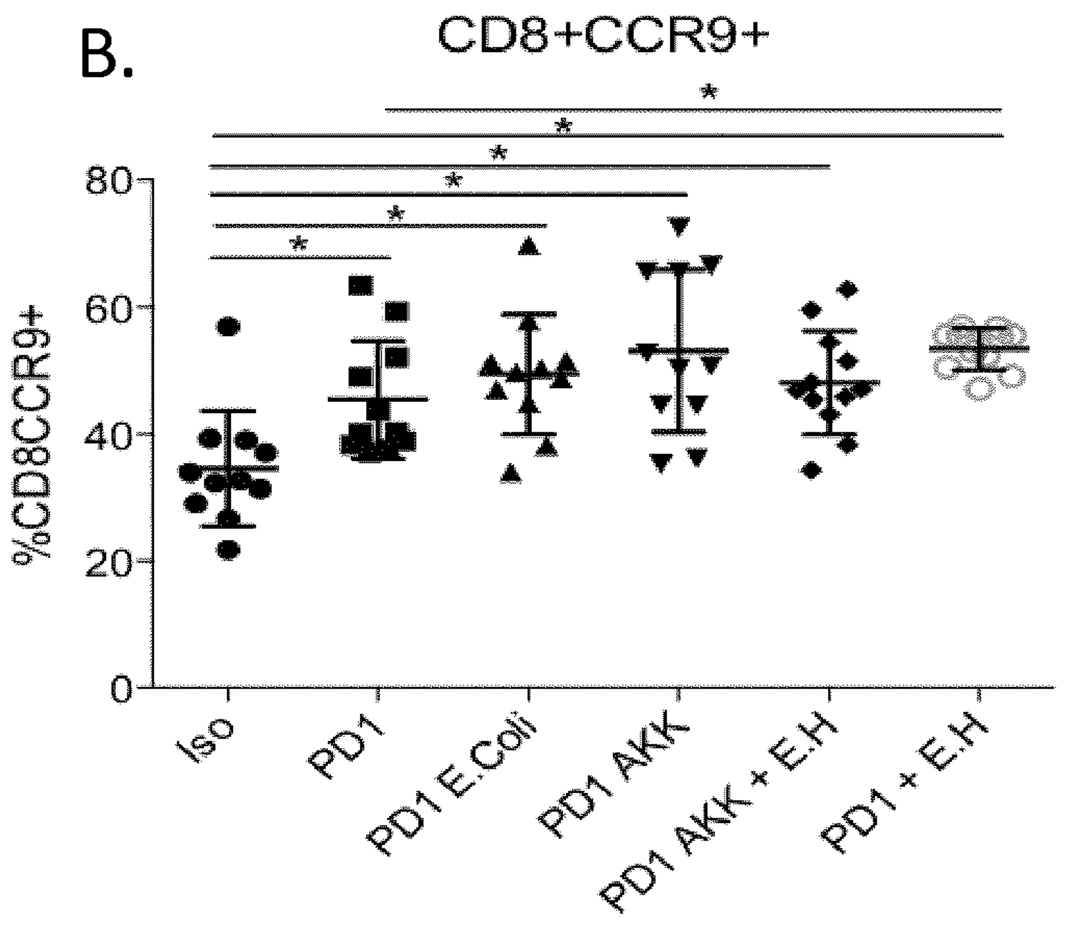
B. Post OncoBax

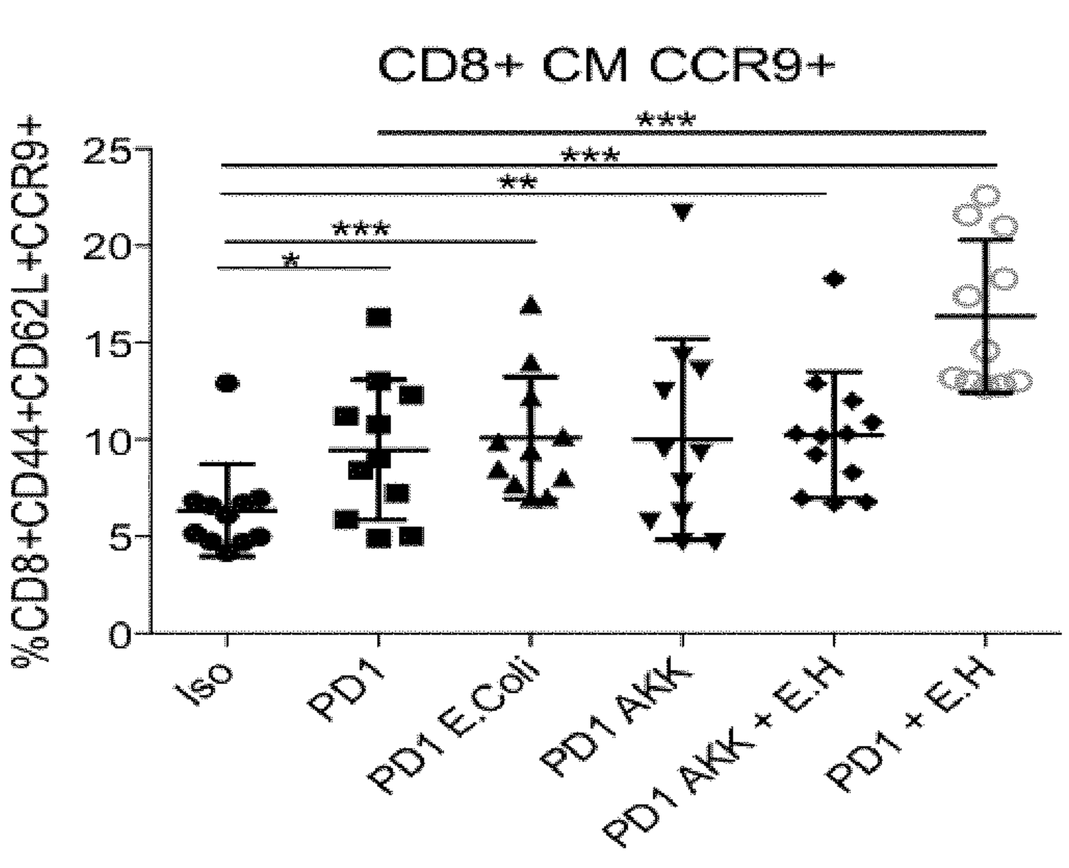
A.


CD4+ Naive CCR9+
%CD4+CCR9+CD44-CD62L+CCR9+
0
2
4
6
*
*
*
*
**
*
Iso
PD1
PD1 E.Coli
PD1 AKK
PD1 AKK + E.H
PD1 + E.H


CD4+ CM CCR9+
%CD4+CD44+CD62L+CCR9+
0
10
20
30
*
*
*
*
*
*
*
Iso
PD1
PD1 E.Coli
PD1 AKK
PD1 AKK + E.H
PD1 + E.H

B.


CD8+CCR9+
%CD8CCR9+
0
20
40
60
80
*
*
*
*
*
*
Iso
PD1
PD1 E.Coli
PD1 AKK
PD1 AKK + E.H
PD1 + E.H


CD8+ CM CCR9+
%CD8+CD44+CD62L+CCR9+
0
5
10
15
20
25
*
***
**
***
***
Iso
PD1
PD1 E.Coli
PD1 AKK
PD1 AKK + E.H
PD1 + E.H

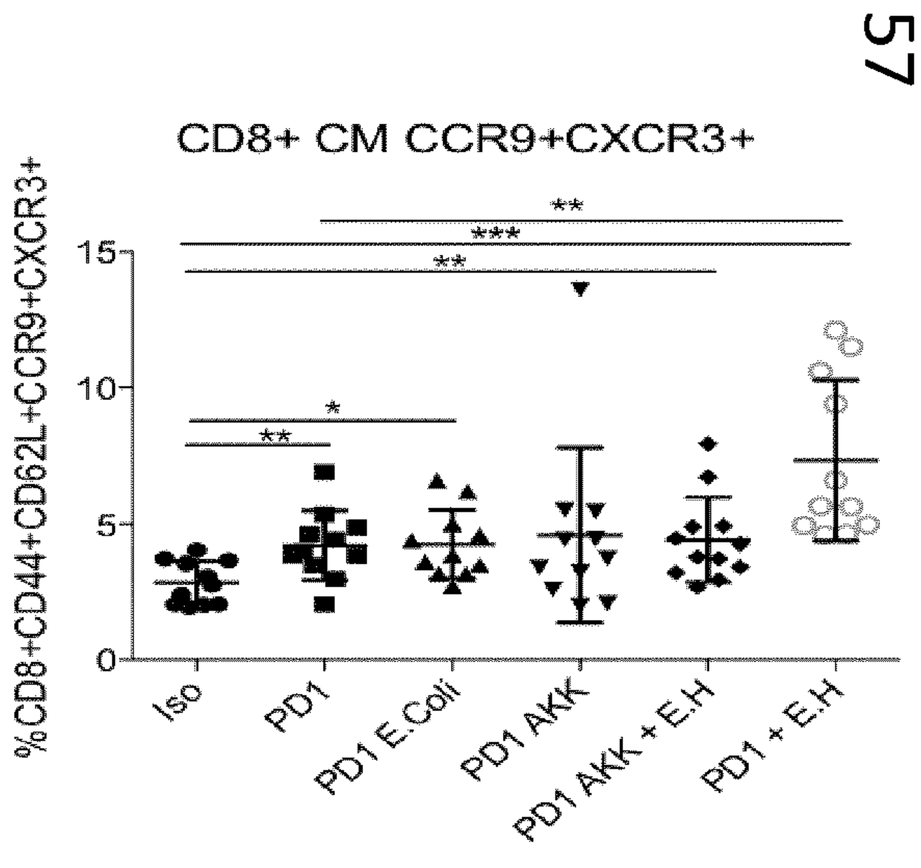
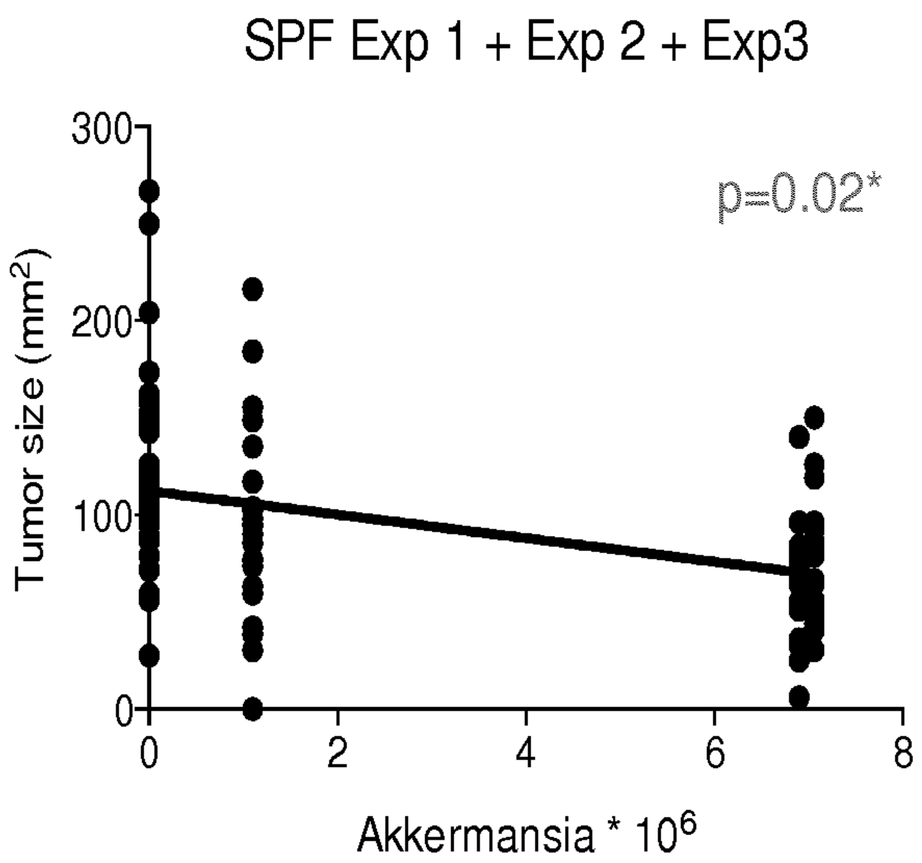
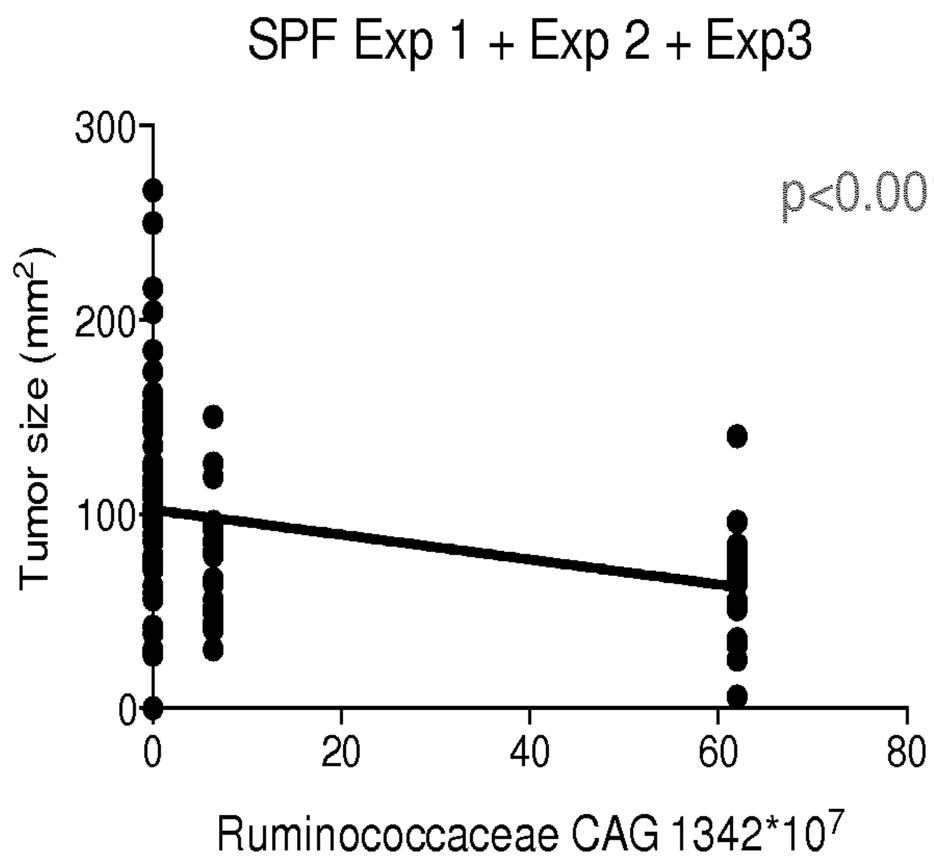
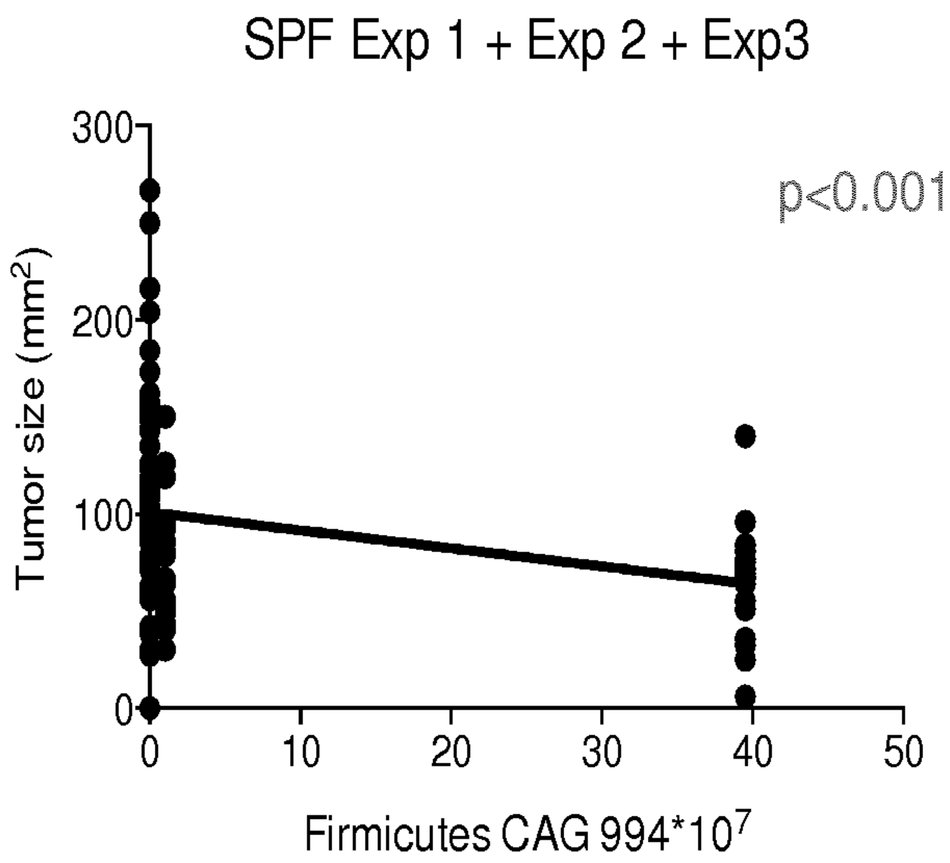
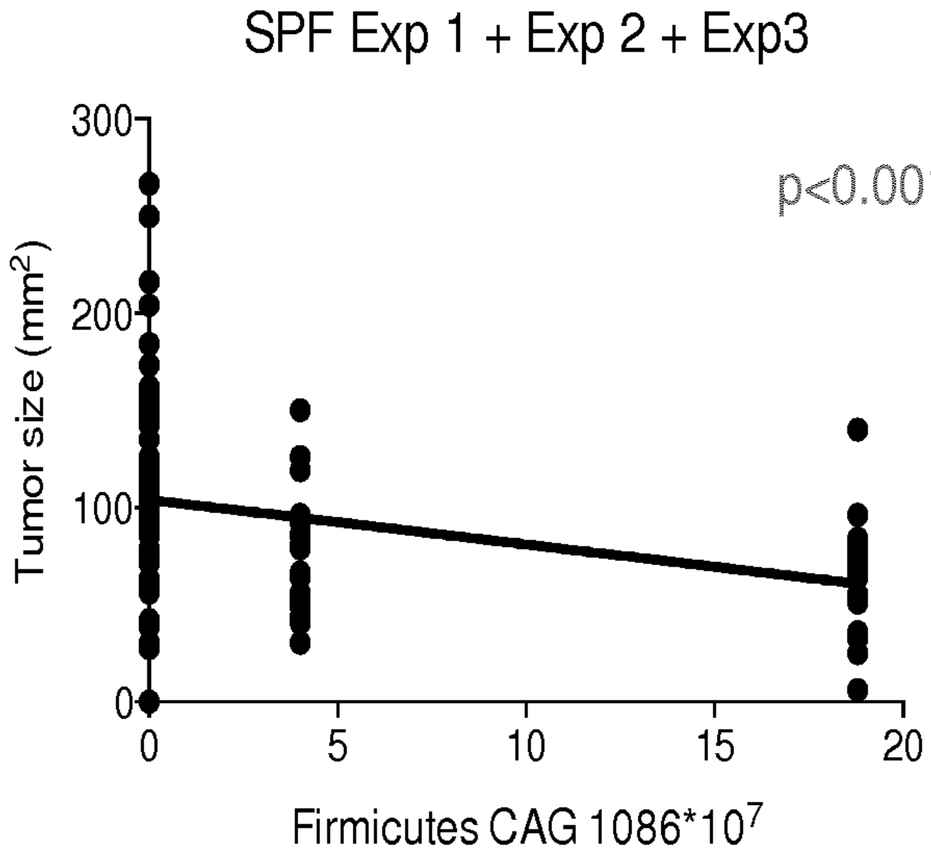

CD8+ CM CCR9+CXCR3+
%CD8+CD44+CD62L+CCR9+CXCR3+
0
5
10
15
**
***
**
*
**
Iso
PD1
PD1 E.Coli
PD1 AKK
PD1 AKK + E.H
PD1 + E.H

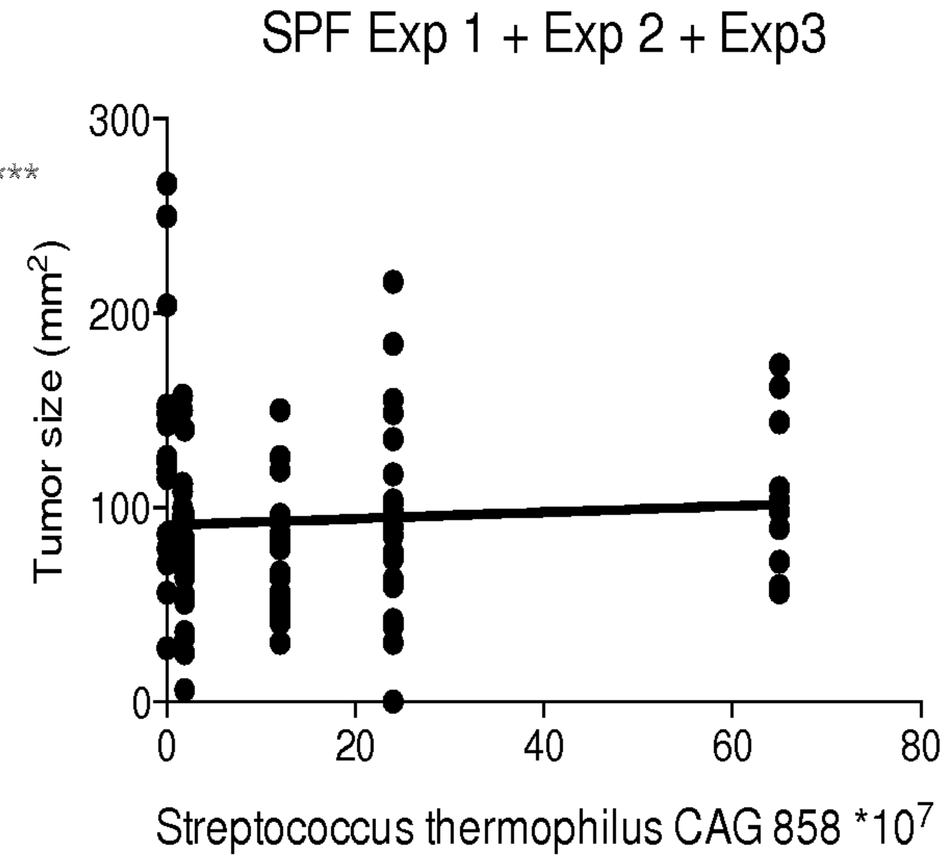
Figure 35


SPF Exp 1 + Exp 2 + Exp3
p=0.02*
Tumor size (mm2)
Akkermansia * 10^6


SPF Exp 1 + Exp 2 + Exp3
p<0.001 ***
Tumor size (mm2)
Ruminococcaceae CAG 1342*10^7


SPF Exp 1 + Exp 2 + Exp3
p<0.001 ***
Tumor size (mm2)
Firmicutes CAG 994*10^7


SPF Exp 1 + Exp 2 + Exp3
p<0.001 ***
Tumor size (mm2)
Firmicutes CAG 1086*10^7


SPF Exp 1 + Exp 2 + Exp3
Tumor size (mm2)
Streptococcus thermophilus CAG 858 *10^7

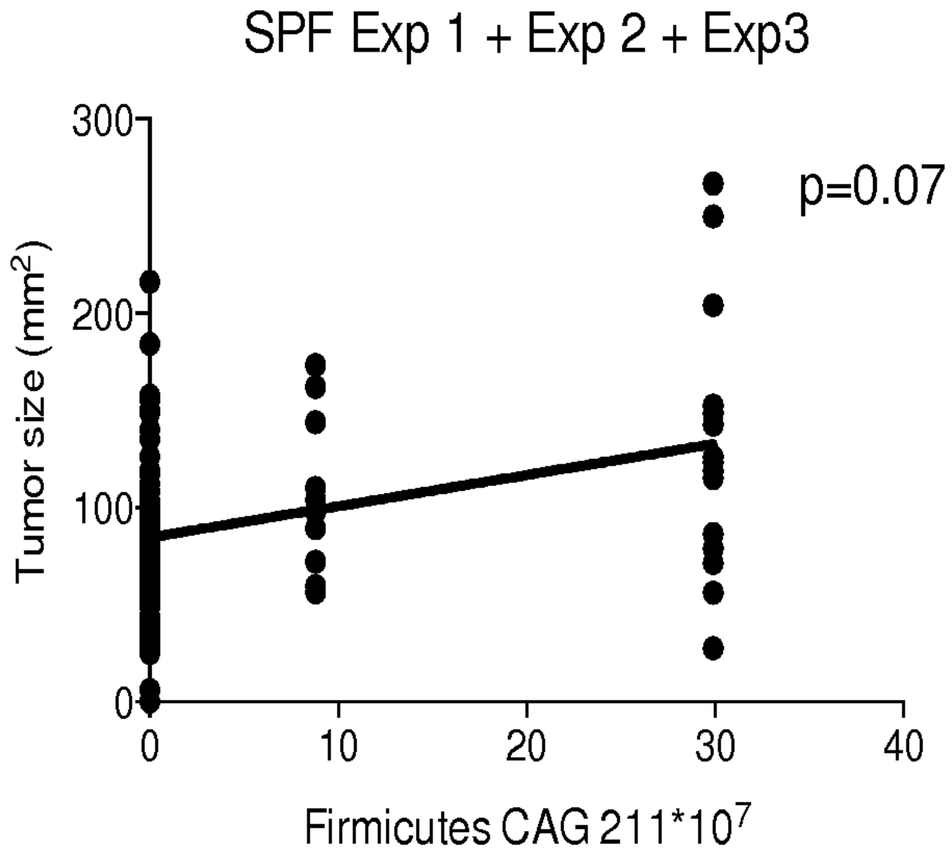
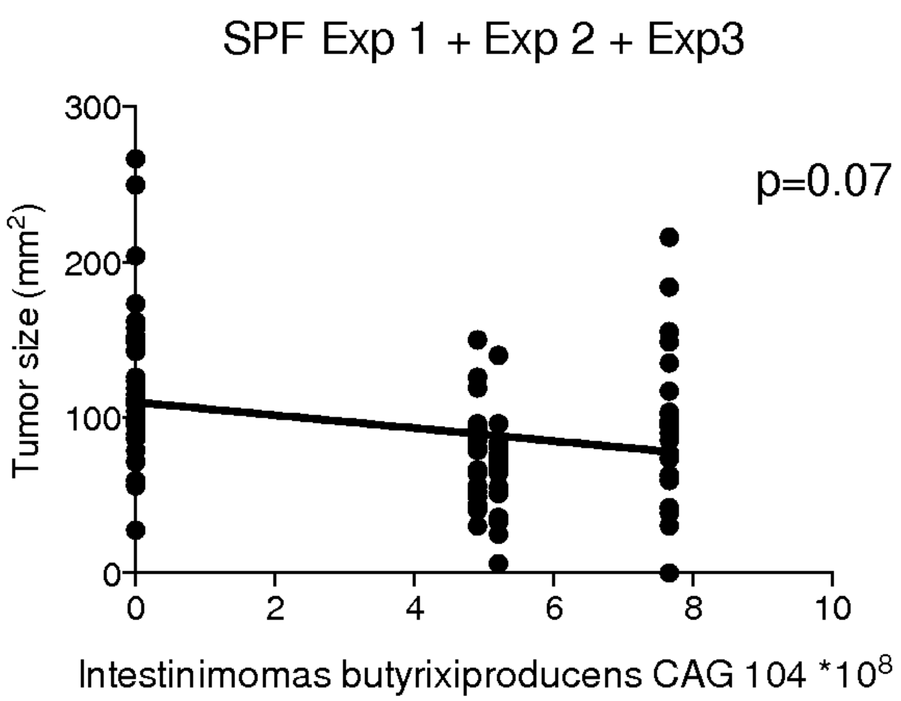
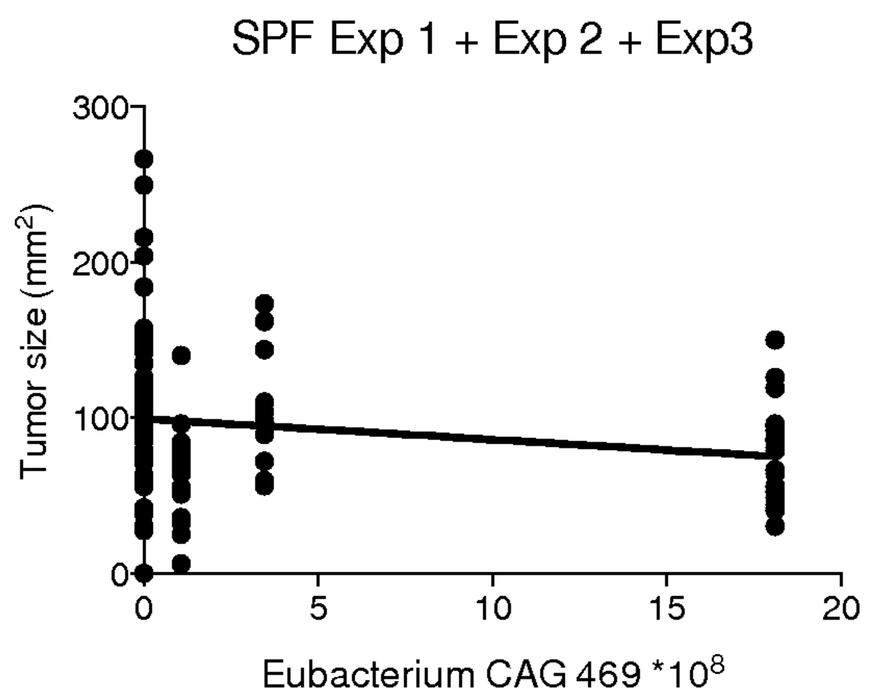
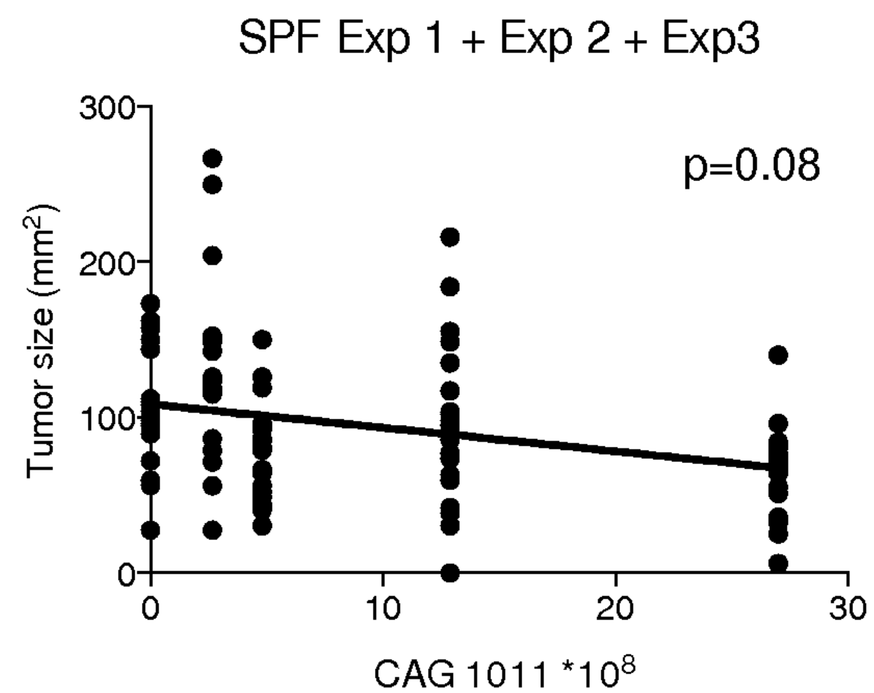
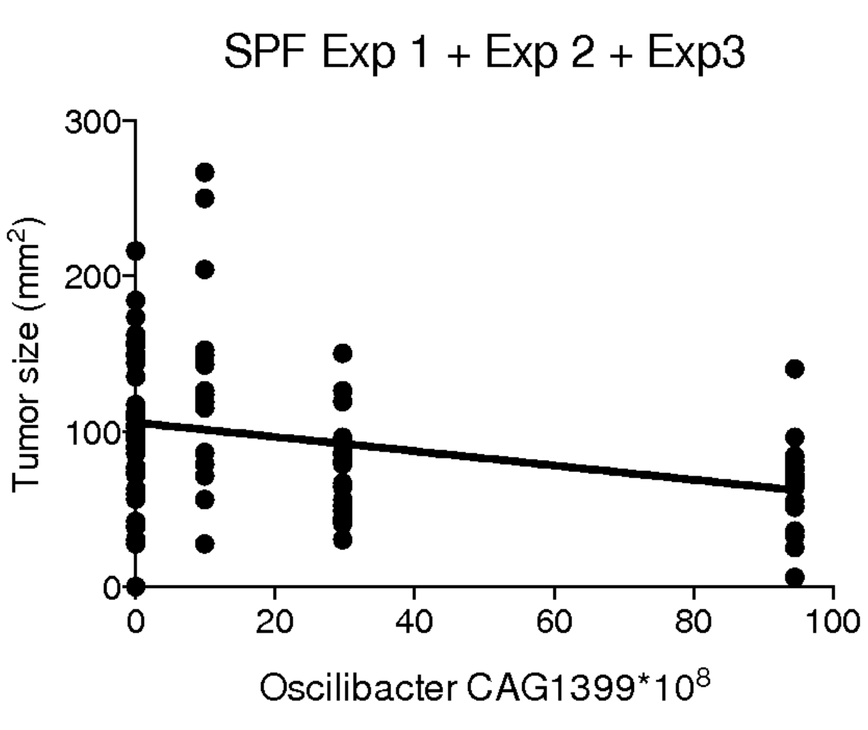

SPF Exp 1 + Exp 2 + Exp3
p=0.07
Tumor size (mm2)
Firmicutes CAG 211*10^7

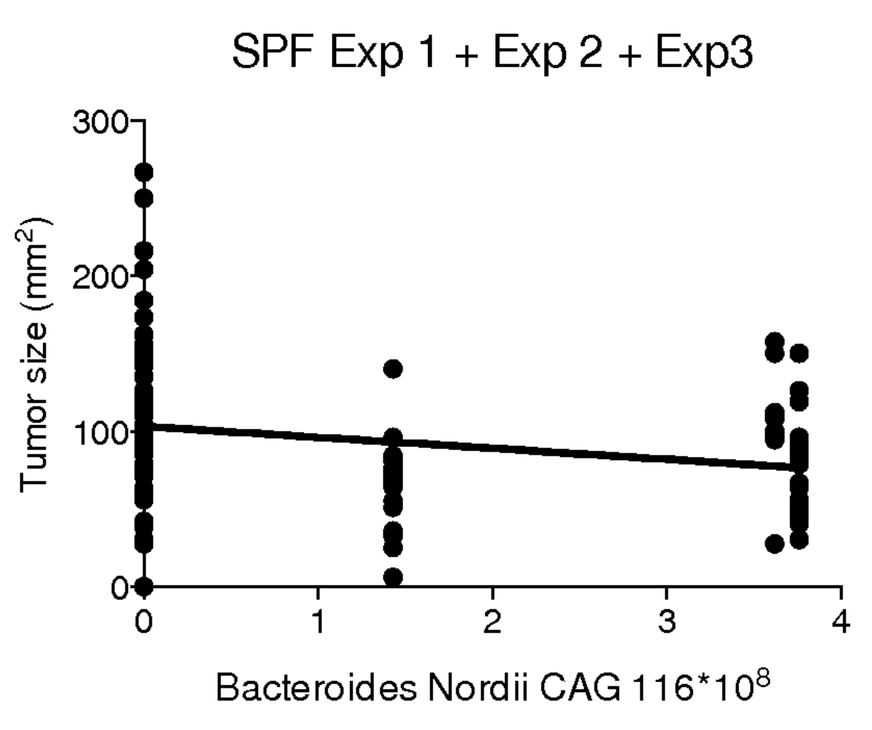
Figure 36A


SPF Exp 1 + Exp 2 + Exp3
p=0.07
Tumor size (mm2)
300
200
100
0
0
2
4
6
8
10
Intestinimomas butyrixiproducens CAG 104 *10^8


SPF Exp 1 + Exp 2 + Exp3
Tumor size (mm2)
300
200
100
0
0
5
10
15
20
Eubacterium CAG 469 *10^8


SPF Exp 1 + Exp 2 + Exp3
p=0.08
Tumor size (mm2)
300
200
100
0
0
10
20
30
CAG 1011 *10^8


SPF Exp 1 + Exp 2 + Exp3
Tumor size (mm2)
300
200
100
0
0
20
40
60
80
100
Oscilibacter CAG1399*10^8


SPF Exp 1 + Exp 2 + Exp3
Tumor size (mm2)
300
200
100
0
0
1
2
3
4
Bacteroides Nordii CAG 116*10^8

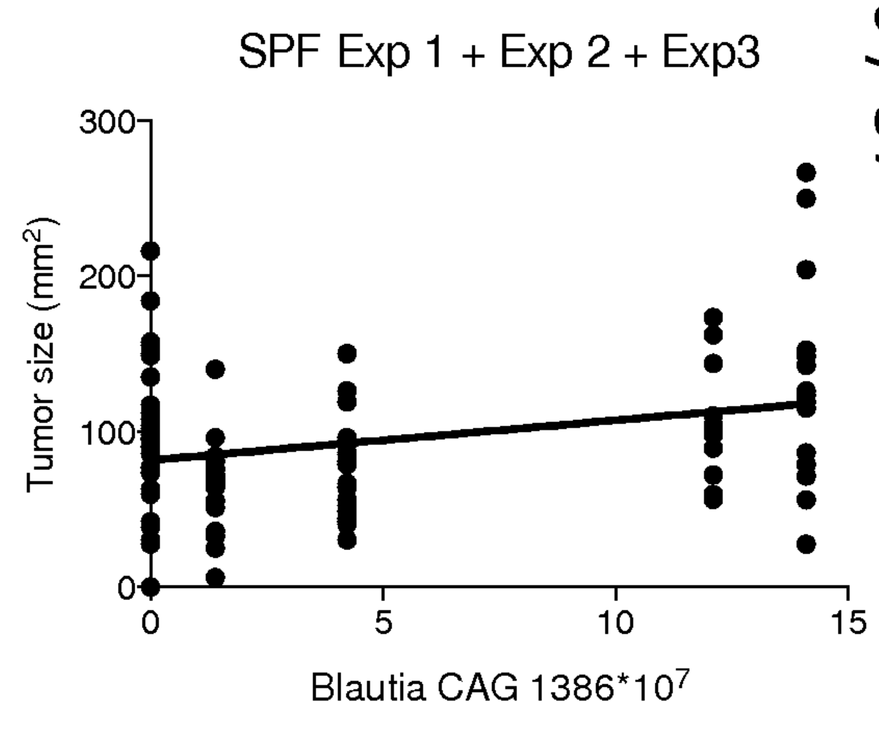

SPF Exp 1 + Exp 2 + Exp3
Tumor size (mm2)
300
200
100
0
0
5
10
15
Blautia CAG 1386*10^7

Figure 36B

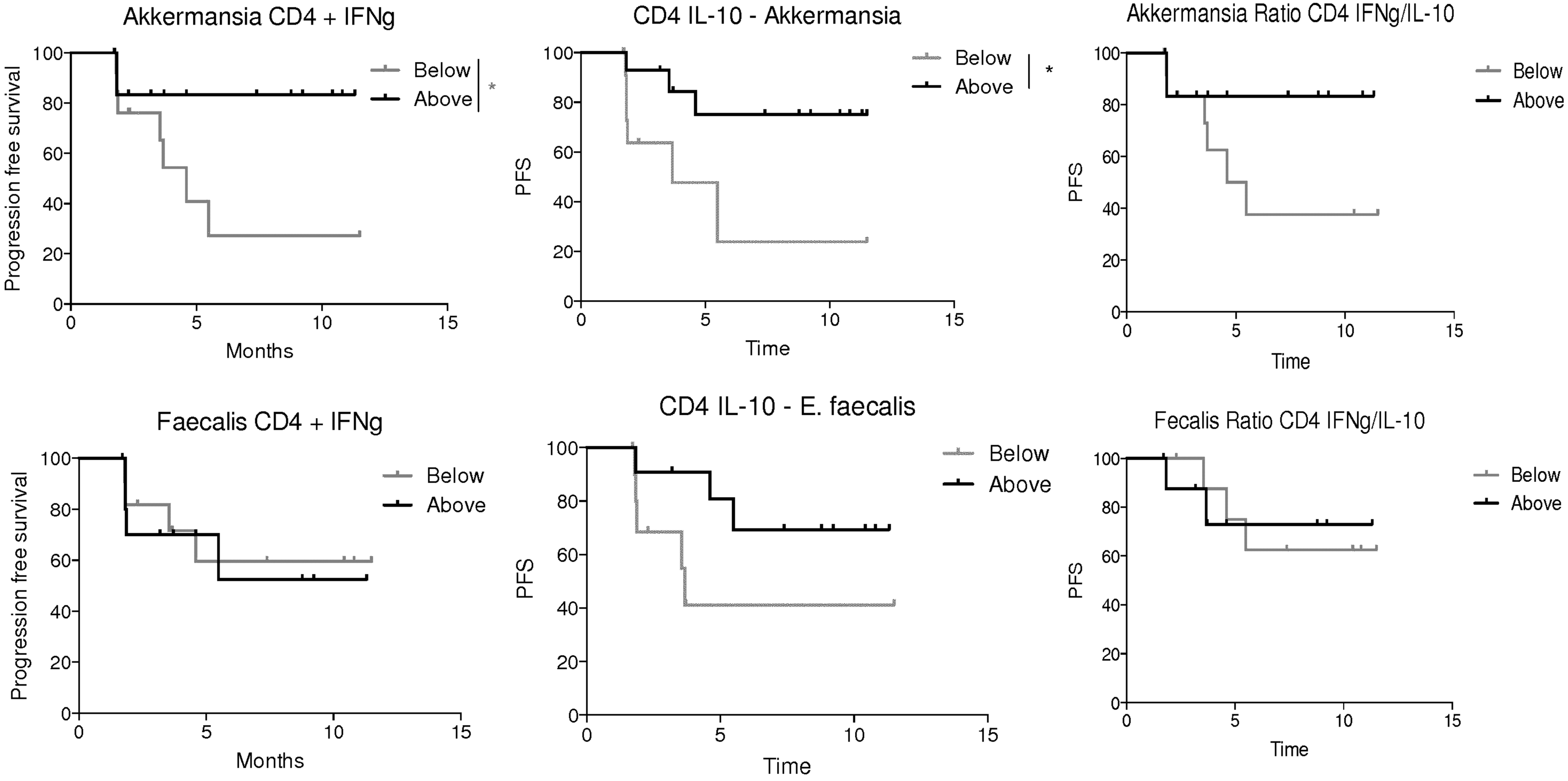

Akkermansia CD4 + IFNg
Progression free survival
Months
Below
Above
*
CD4 IL-10 - Akkermansia
PFS
Time
Below
Above
*
Akkermansia Ratio CD4 IFNg/IL-10
PFS
Time
Below
Above
Faecalis CD4 + IFNg
Progression free survival
Months
Below
Above
CD4 IL-10 - E. faecalis
PFS
Time
Below
Above
Fecalis Ratio CD4 IFNg/IL-10
PFS
Time
Below
Above

Figure 37

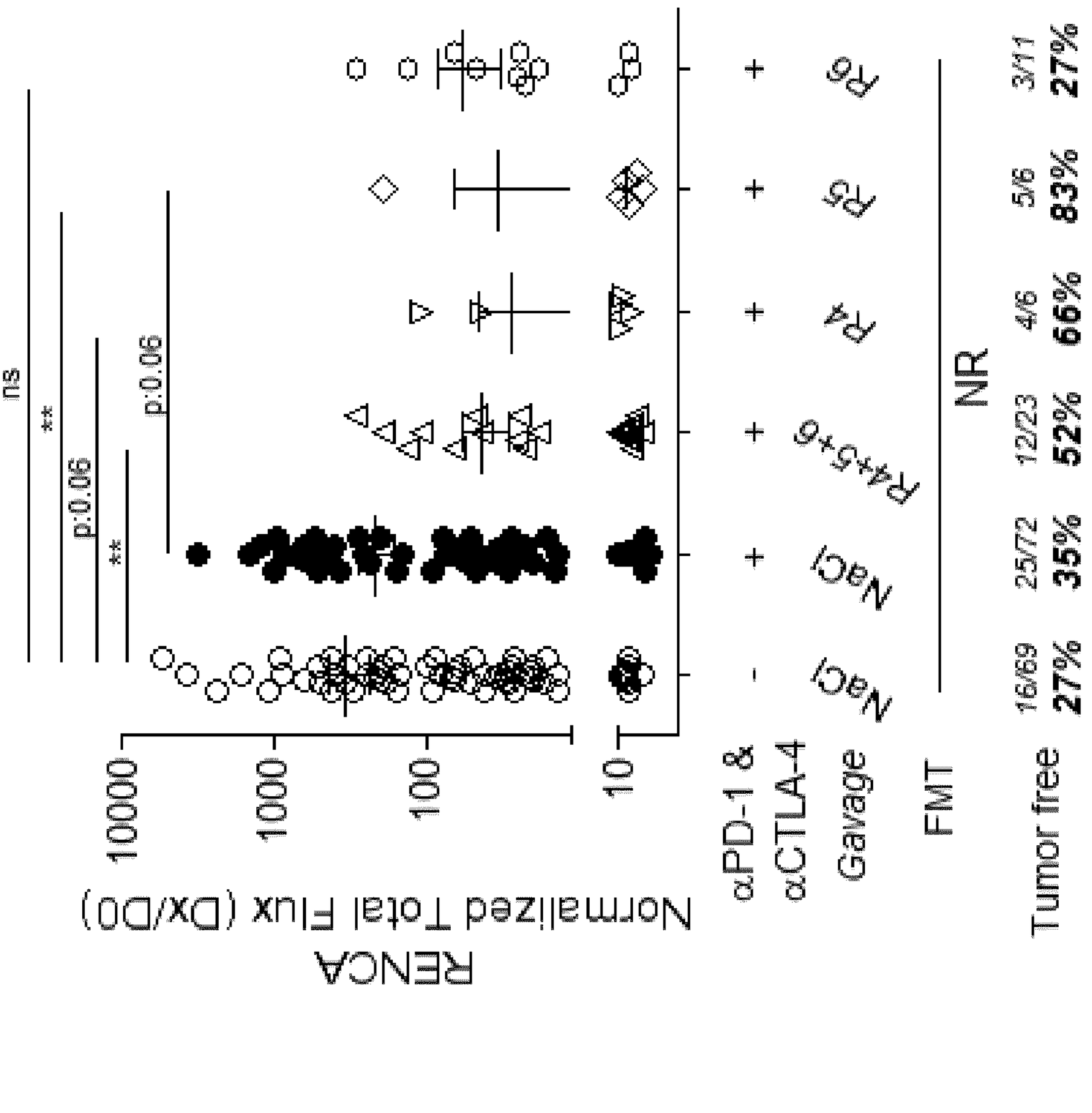
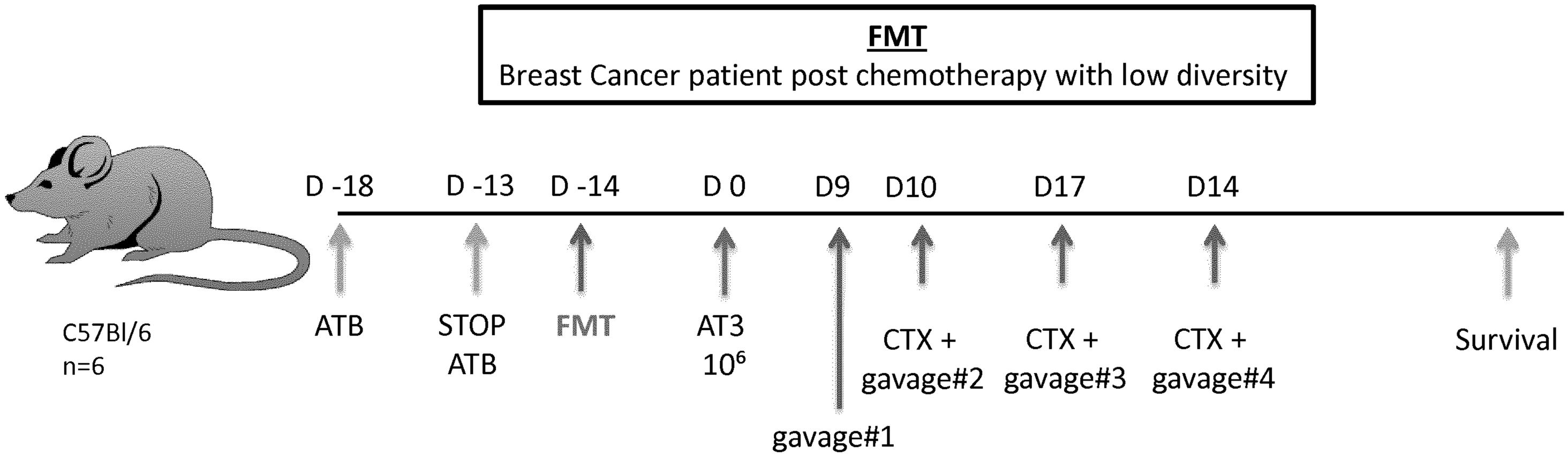

RENCA
Normalized Total Flux (Dx/D0)
10000
1000
100
10
ns
**
p:0.06
p:0.06
**
αPD-1 &
αCTLA-4
Gavage
FMT
Naïve
Naïve
R4+5+6
R4
R5
R6
NR
Tumor free
16/69
27%
25/72
35%
12/23
52%
4/6
66%
5/6
83%
3/11
27%

Figure 38



Groups

1. FMT Healthy volunteer + PBS (n=6)
2. FMT Healthy volunteer + CTX (n=6)

1. FMT Breast Ca patient #1 + PBS (n=6)
2. FMT Breast Ca patient #1 + CTX (n=6)
3. Co-housing FMT Breast Ca patient #1 (n=6) + FMT Healthy volunteer (n=6) + CTX
4. FMT Breast Ca patient #1 (n=6) + Oral gavage x 4 from Healthy volunteer + CTX

1. FMT Breast Ca patient #2 + PBS (n=6)
2. FMT Breast Ca patient #2 + CTX (n=6)
3. Co-housing FMT Breast Ca patient #2 (n=6) + FMT Healthy volunteer (n=6) + CTX
4. FMT Breast Ca patient #2 (n=6) + Oral gavage x 4 from Healthy volunteer + CTX

Patient #1 (bad prognosis):
Triple neg, Stage IIb, Ki 67: 35%, Tils: 5%

Patient #2 (good prognosis):
ER/PR Pos, Ki67:5%, Tils: 10%

Figure 39A

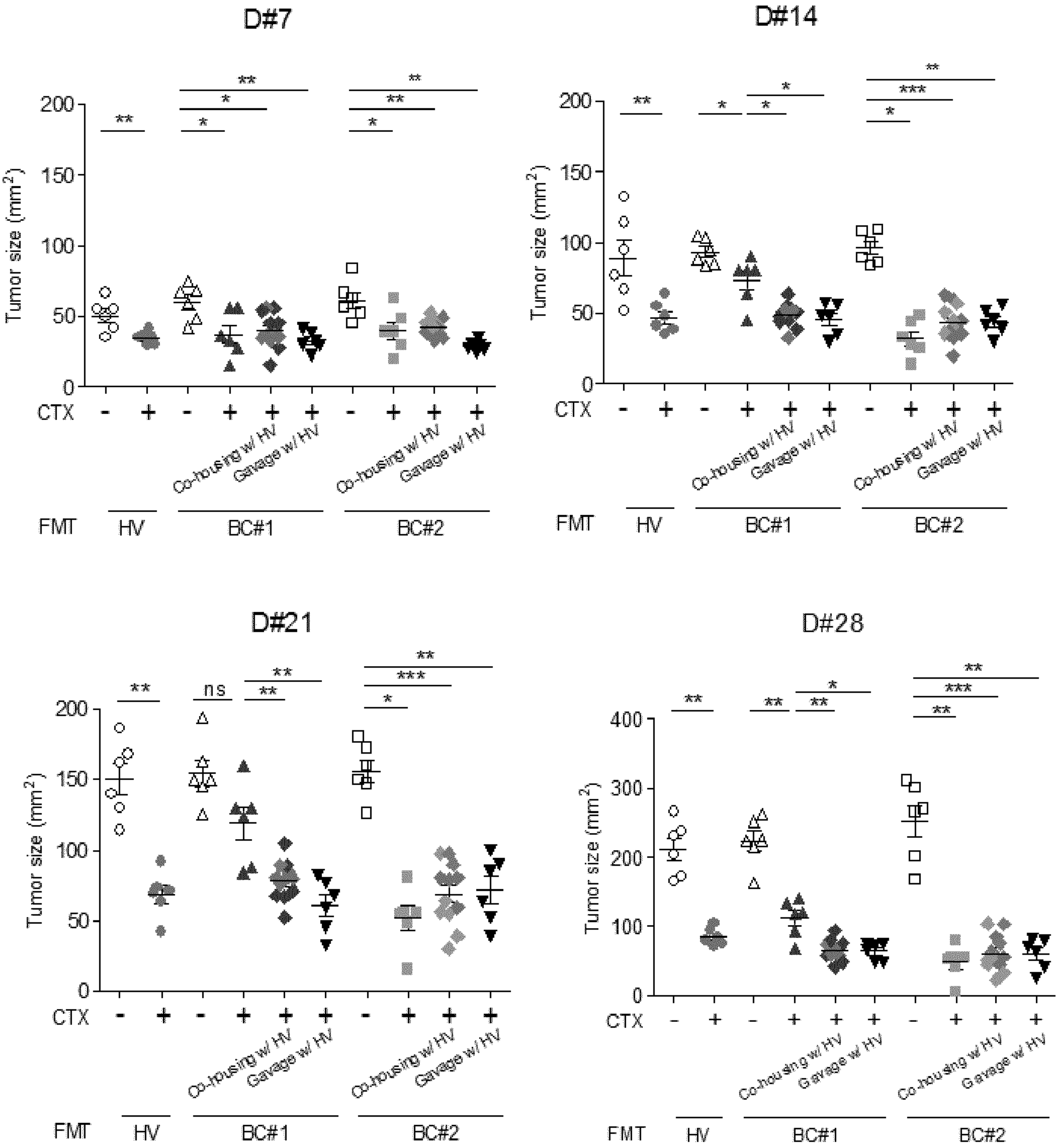

D#7
D#14
D#21
D#28
Tumor size (mm2)
CTX
FMT
HV
BC#1
BC#2
Co-housing w/ HV
Gavage w/ HV
ns

Figure 39B

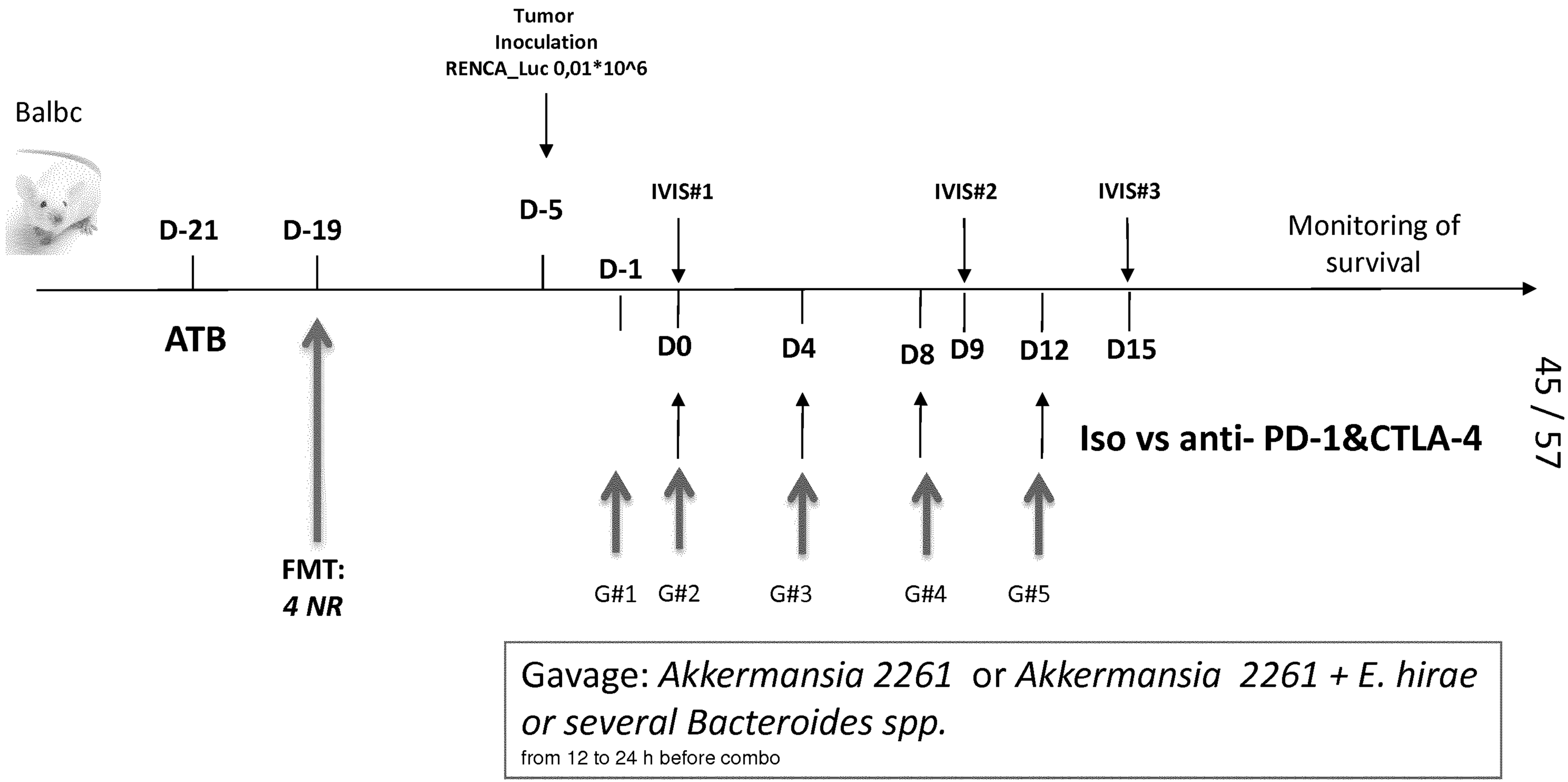

Tumor
Inoculation
RENCA_Luc 0,01*10^6
Balbc
D-21
D-19
D-5
D-1
IVIS#1
IVIS#2
IVIS#3
Monitoring of survival
ATB
D0
D4
D8
D9
D12
D15
45 / 57
Iso vs anti- PD-1&CTLA-4
FMT:
4 NR
G#1
G#2
G#3
G#4
G#5
Gavage: Akkermansia 2261 or Akkermansia 2261 + E. hirae or several Bacteroides spp.
from 12 to 24 h before combo

Figure 40A

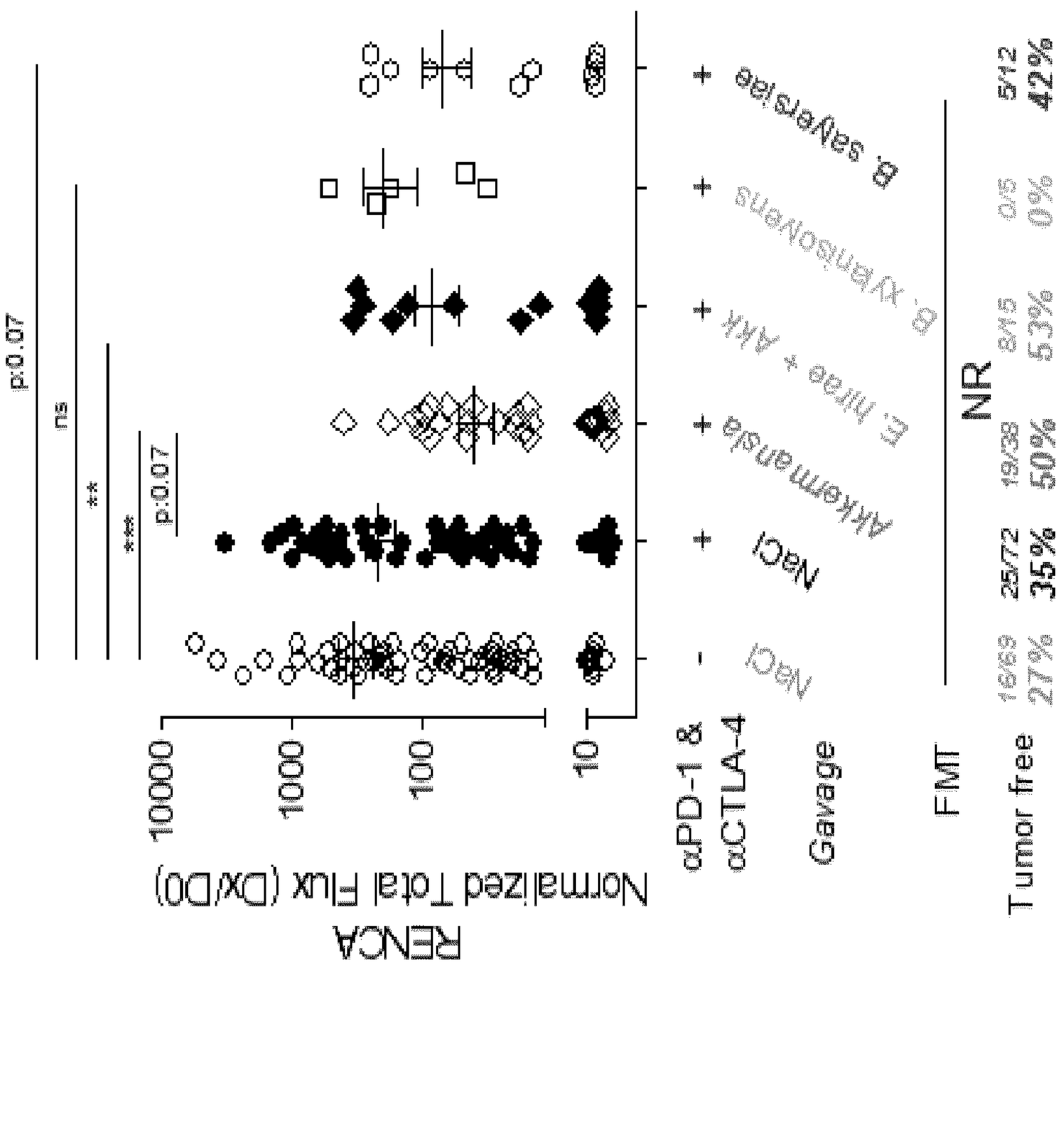

RENCA
Normalized Total Flux (Dx/D0)
10000
1000
100
10
p:0.07
***
**
ns
p:0.07
αPD-1 &
αCTLA-4
Gavage
-
+
+
+
NaCl
NaCl
Akkermansia
E. hirae + AMK
B. xylanisolvens
B. salyersiae
FMT
Tumor free
16/69
27%
25/72
35%
19/38
50%
NR
8/15
5.3%
0/5
0%
5/12
42%

Figure 40B

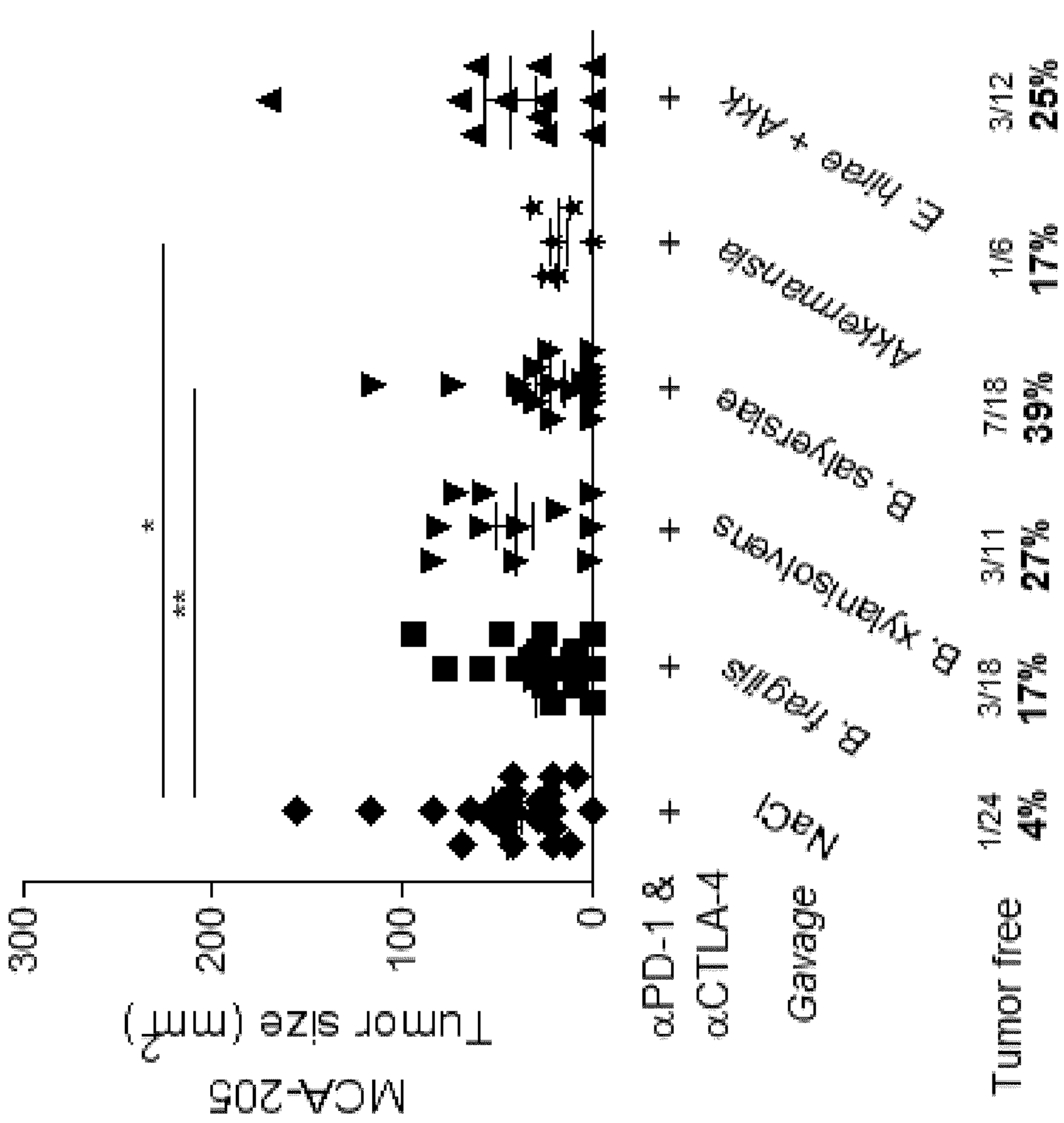
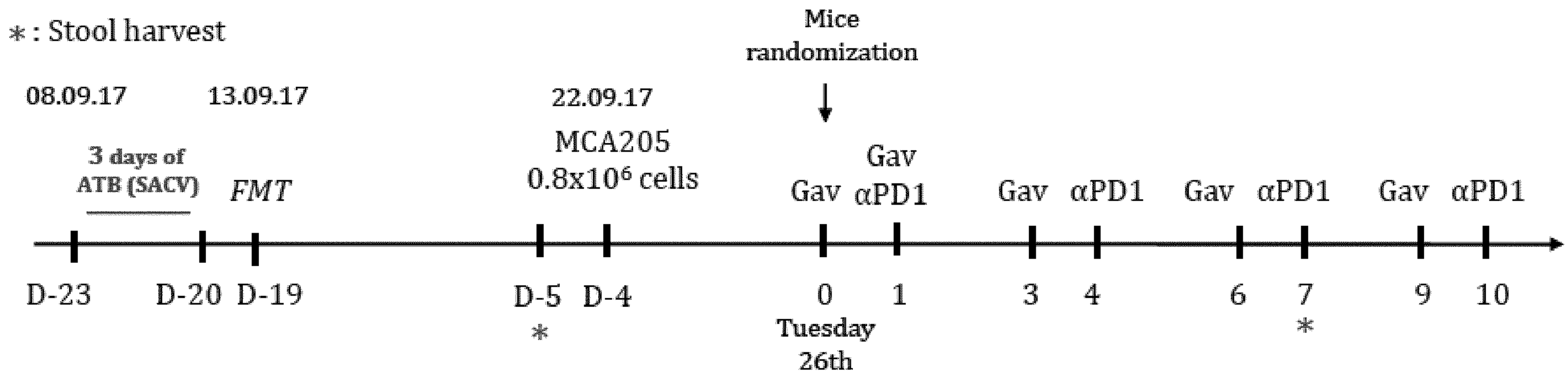

MCA-205
Tumor size (mm²)
300
200
100
0
*
**
αPD-1 &
αCTLA-4
+
+
+
+
Gavage
NaCl
B. fragilis
B. xylanisolvens
B. salyersiae
Akkermansia
C. hiraeo + Akk
Tumor free
1/24
4%
3/18
17%
3/11
27%
7/18
39%
1/6
17%
3/12
25%

Figure 41



FMT: - Isotype 2A3

- αPD1

- αPD1 + *E. hirae* 13144 + IGR4 + IGR7

- αPD1 + *Akk* p2261 + *Akk* p3415

- αPD1 + *Alistipes finegoldii* + *A. oderdonkii*

- αPD1 + *Bacteroides xylanisolvens* + *B. salyersiae*

- αPD1 + *E. hirae* {13144 / IGR7 / IGR4} + *Akk* {p2261 / p3415} + *E. limosum*

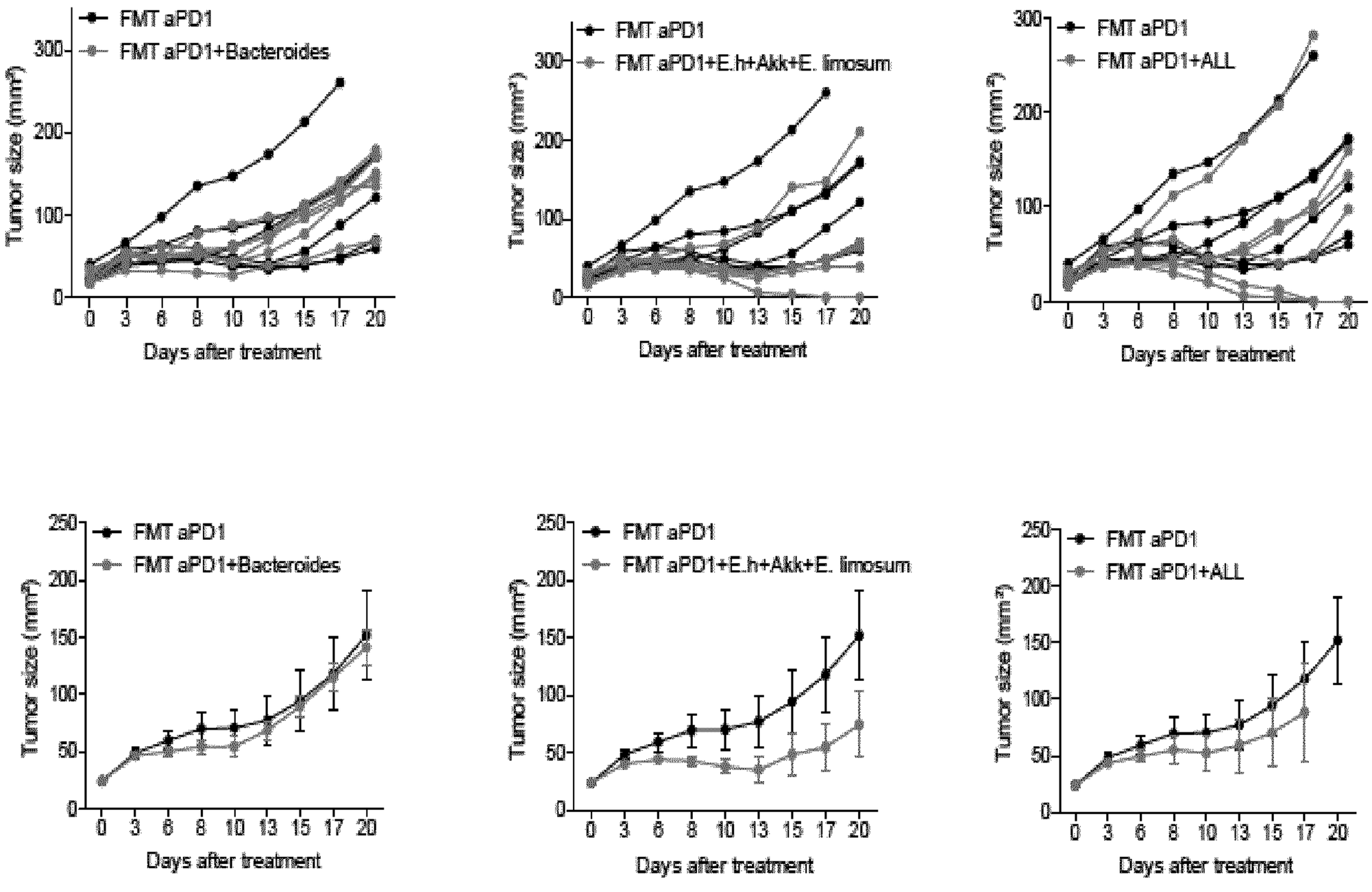
- αPD1 + *E. hirae* {13144 / IGR7 / IGR4} + *Akk* {p2261 / p3415} + *E. limosum* + *Bact.* {*salyersiae* / *xylanisolvens*} + *Alistipes* {*finegoldii* / *oderdonkii*}

E. Hirae & Cie: 10^9 bacteria/100µl

Akk: 10^8 bacteria/100µl

Figure 42A

B.



C.

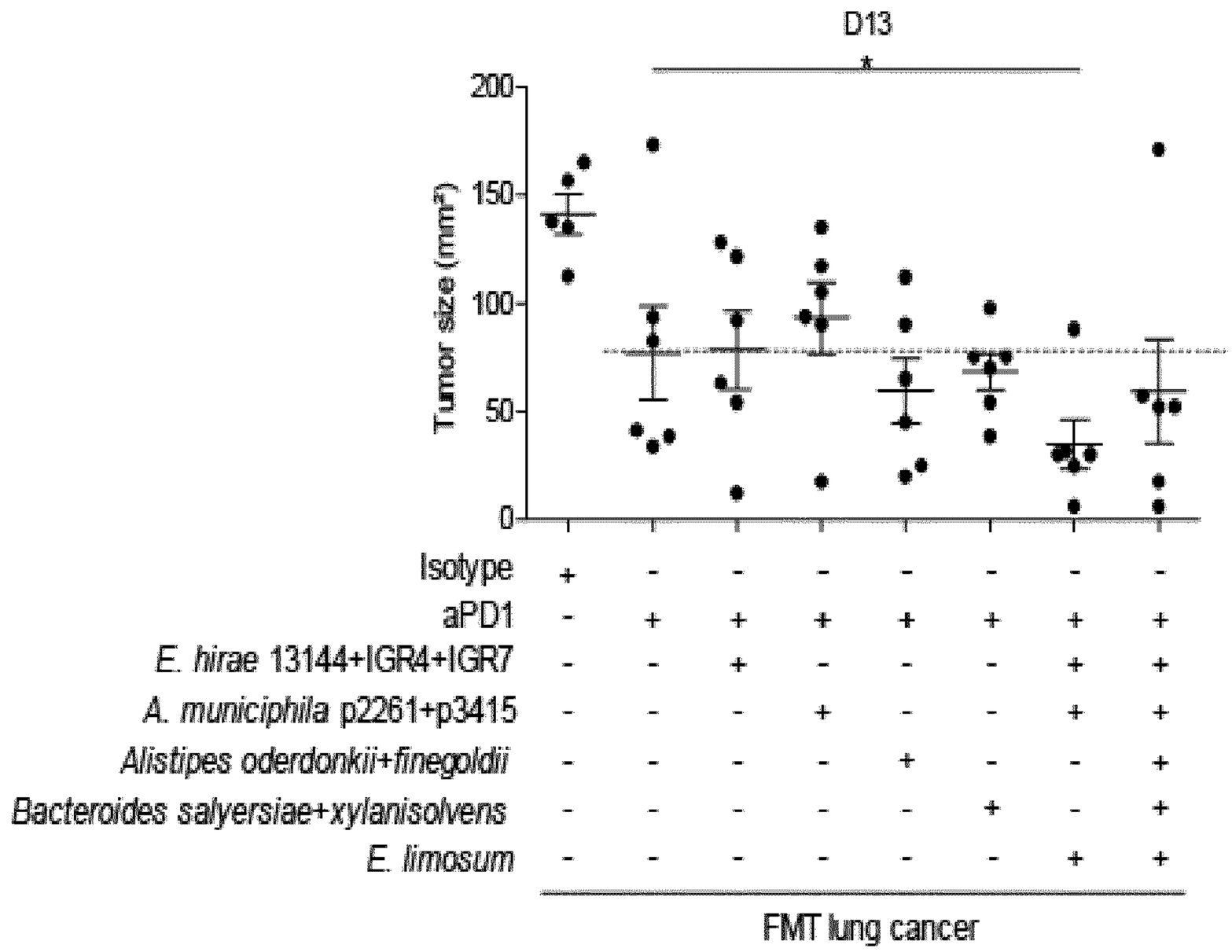


Figure 42B-C

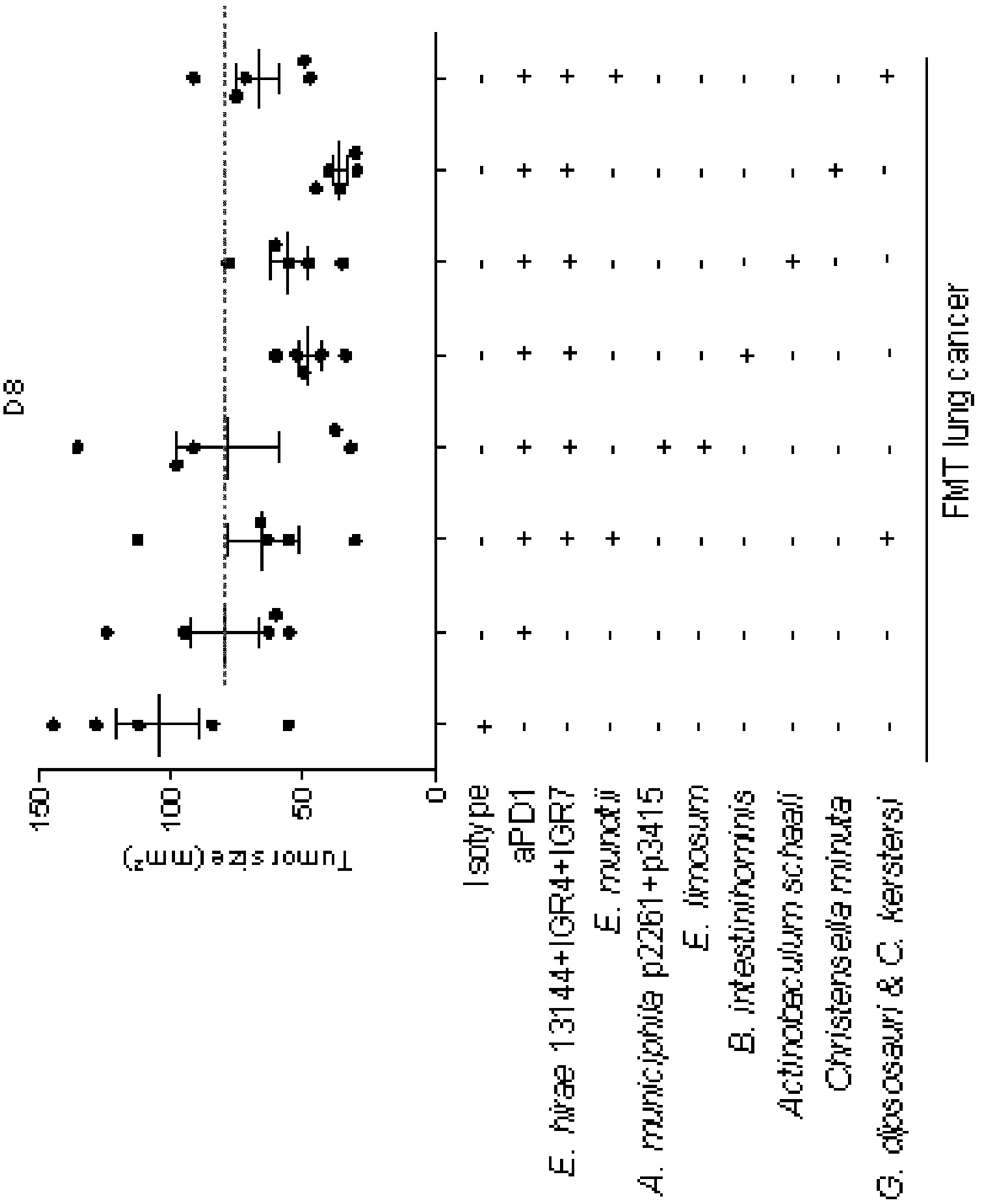
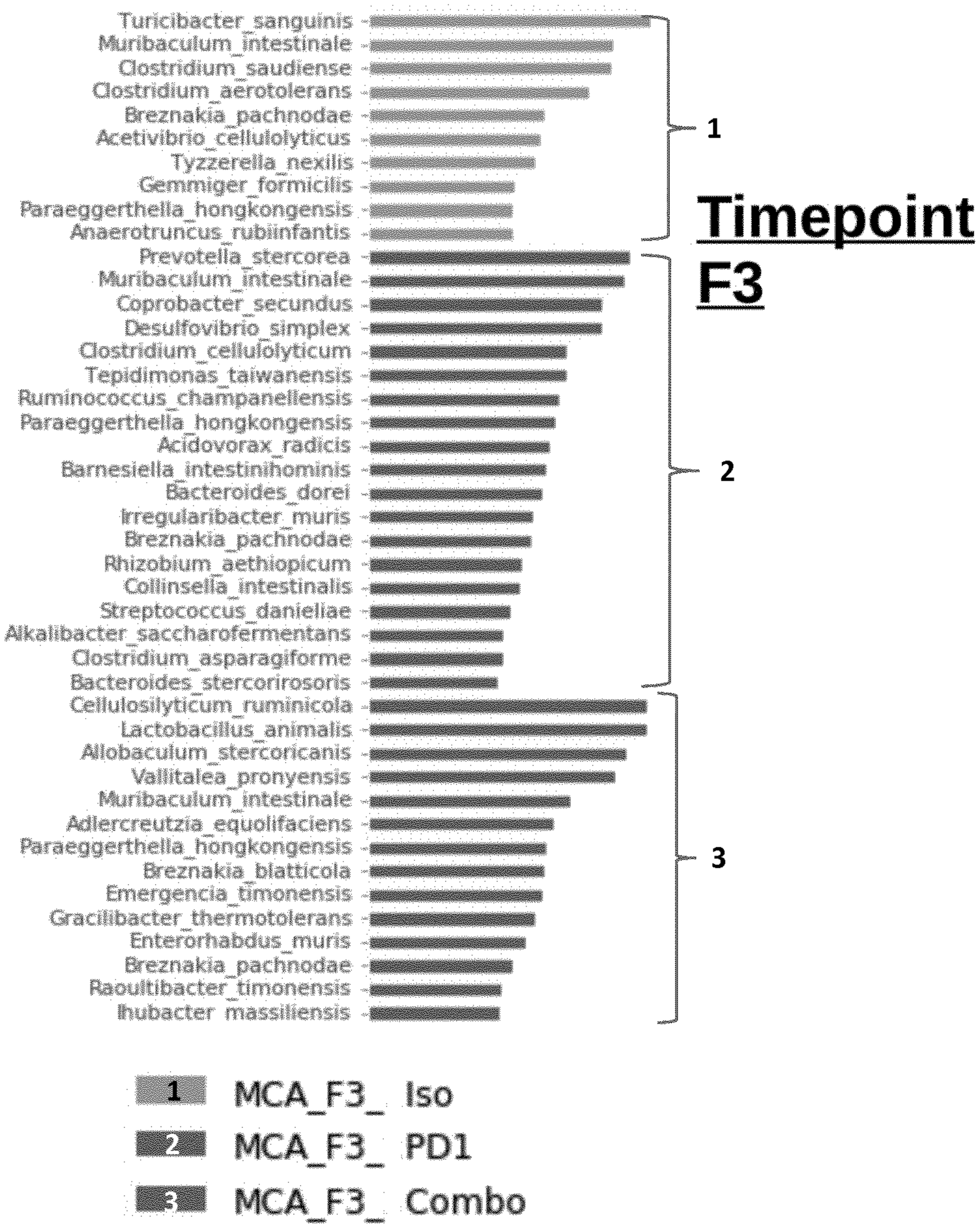
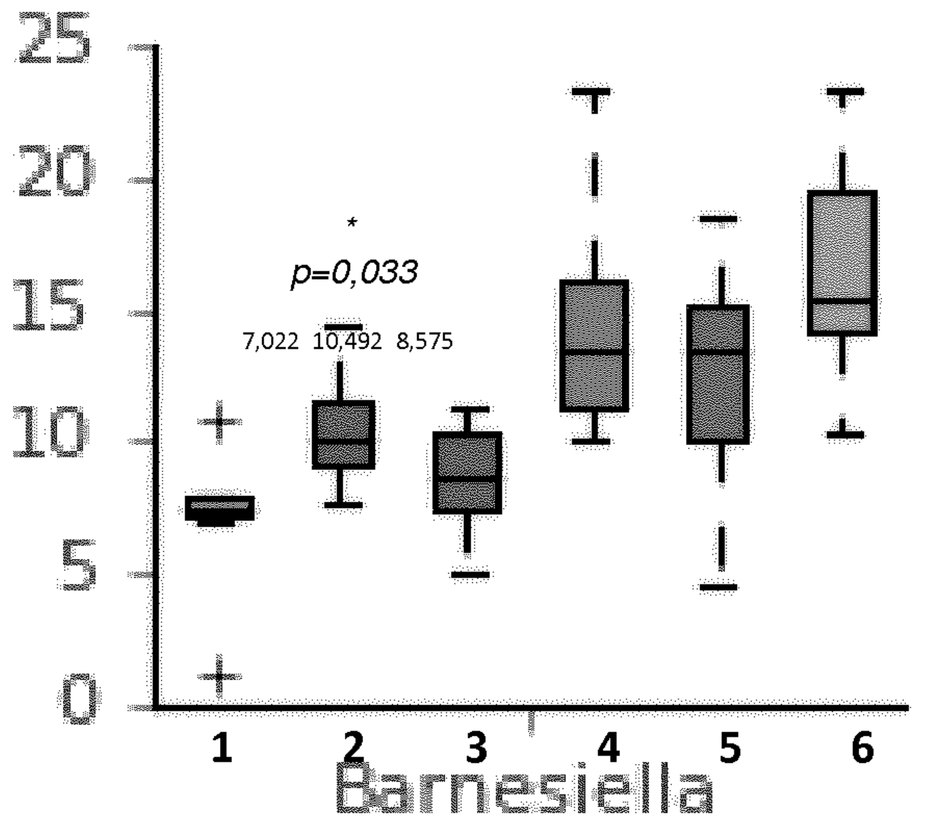

D8
Tumor size (mm²)
150
100
50
0
Isotype
aPD1
E. hirae 13144+IGR4+IGR7
E. rundtii
Enterococcus municipiola p2261+p3415
E. flmosum
B. intestinihominis
Actinobacillum schaali
Christensella minuta
Odoribacter splanchnicus & C. kerstersi
FMT lung cancer

Figure 43

A


Turicibacter_sanguinis
Muribaculum_intestinale
Clostridium_saudiense
Clostridium_aerotolerans
Breznakia_pachnodae
Acetivibrio_cellulolyticus
Tyzzerella_nexilis
Gemmiger_formicilis
Paraeggerthella_hongkongensis
Anaerotruncus_rubiinfantis
Prevotella_stercorea
Muribaculum_intestinale
Coprobacter_secundus
Desulfovibrio_simplex
Clostridium_cellulolyticum
Tepidimonas_taiwanensis
Ruminococcus_champanellensis
Paraeggerthella_hongkongensis
Acidovorax_radicis
Barnesiella_intestinihominis
Bacteroides_dorei
Irregularibacter_muris
Breznakia_pachnodae
Rhizobium_aethiopicum
Collinsella_intestinalis
Streptococcus_danieliae
Alkalibacter_saccharofermentans
Clostridium_asparagiforme
Bacteroides_stercorirosoris
Cellulosilyticum_ruminicola
Lactobacillus_animalis
Allobaculum_stercoricanis
Vallitalea_pronyensis
Muribaculum_intestinale
Adlercreutzia_equolifaciens
Paraeggerthella_hongkongensis
Breznakia_blatticola
Emergencia_timonensis
Gracilibacter_thermotolerans
Enterorhabdus_muris
Breznakia_pachnodae
Raoultibacter_timonensis
Ihubacter_massiliensis
1
2
3
Timepoint F3
1 MCA_F3_ Iso
2 MCA_F3_ PD1
3 MCA_F3_ Combo

B


25
20
15
10
5
0
p=0,033
7,022
10,492
8,575
1
2
3
4
5
6
Barnesiella

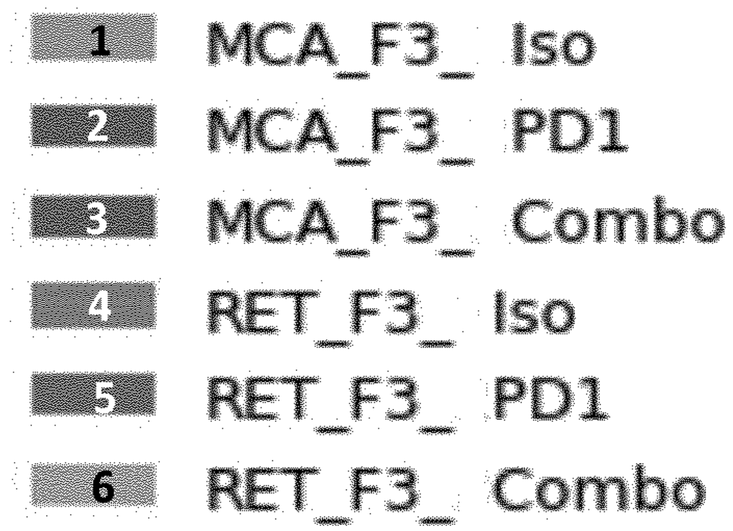
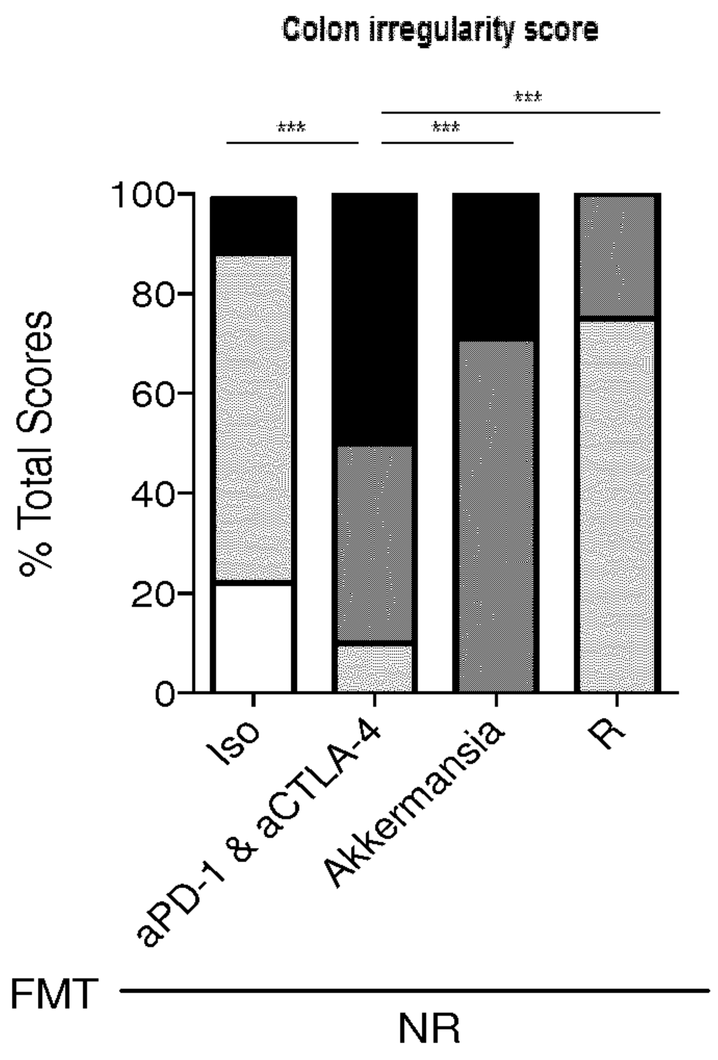
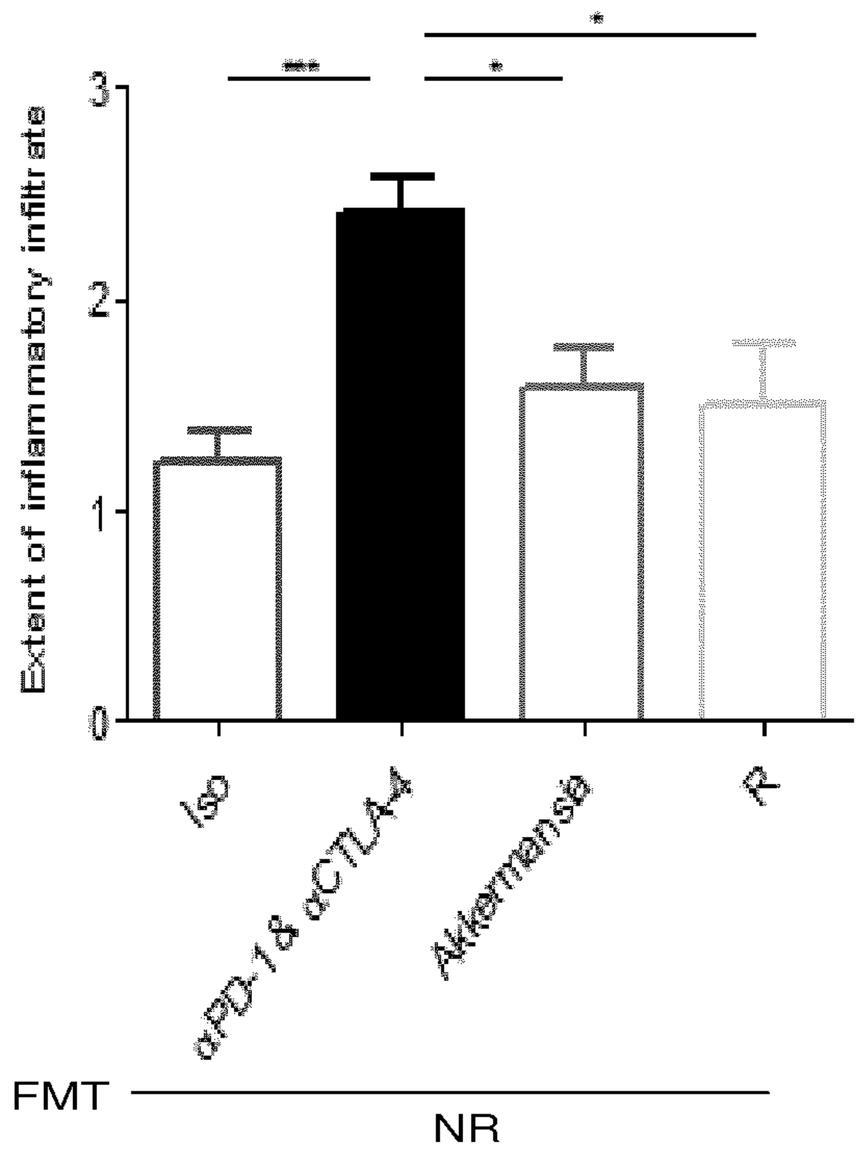
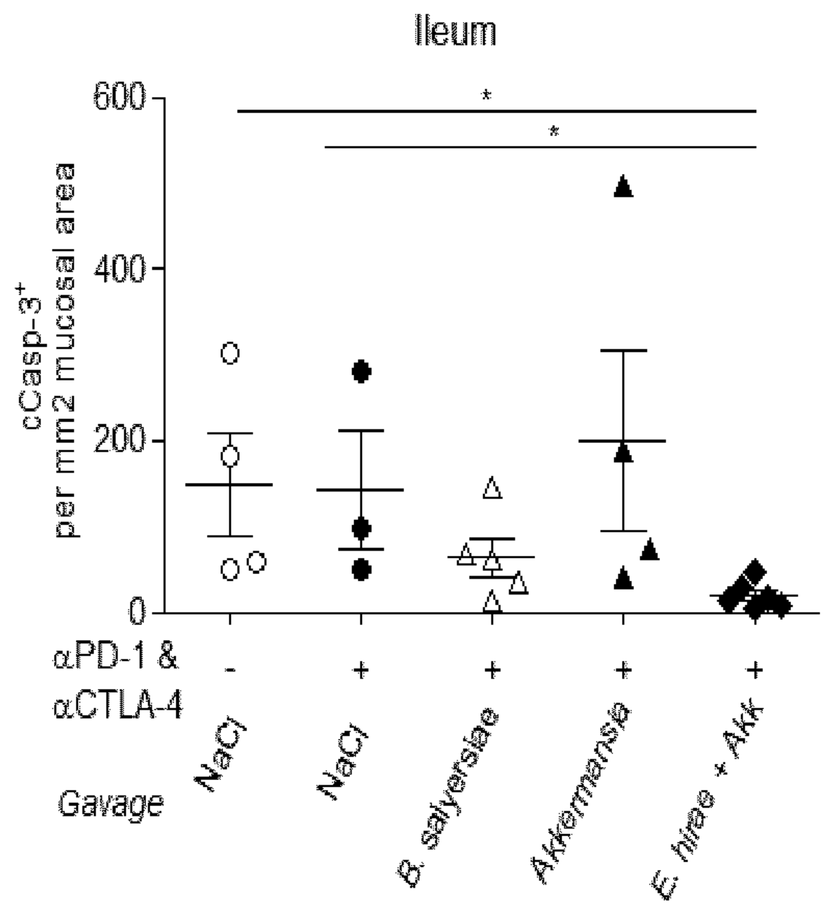

1 MCA_F3_ Iso
2 MCA_F3_ PD1
3 MCA_F3_ Combo
4 RET_F3_ Iso
5 RET_F3_ PD1
6 RET_F3_ Combo

Figure 44







R: compensation from responding patient

Figure 45

Samples to be sent n = 109

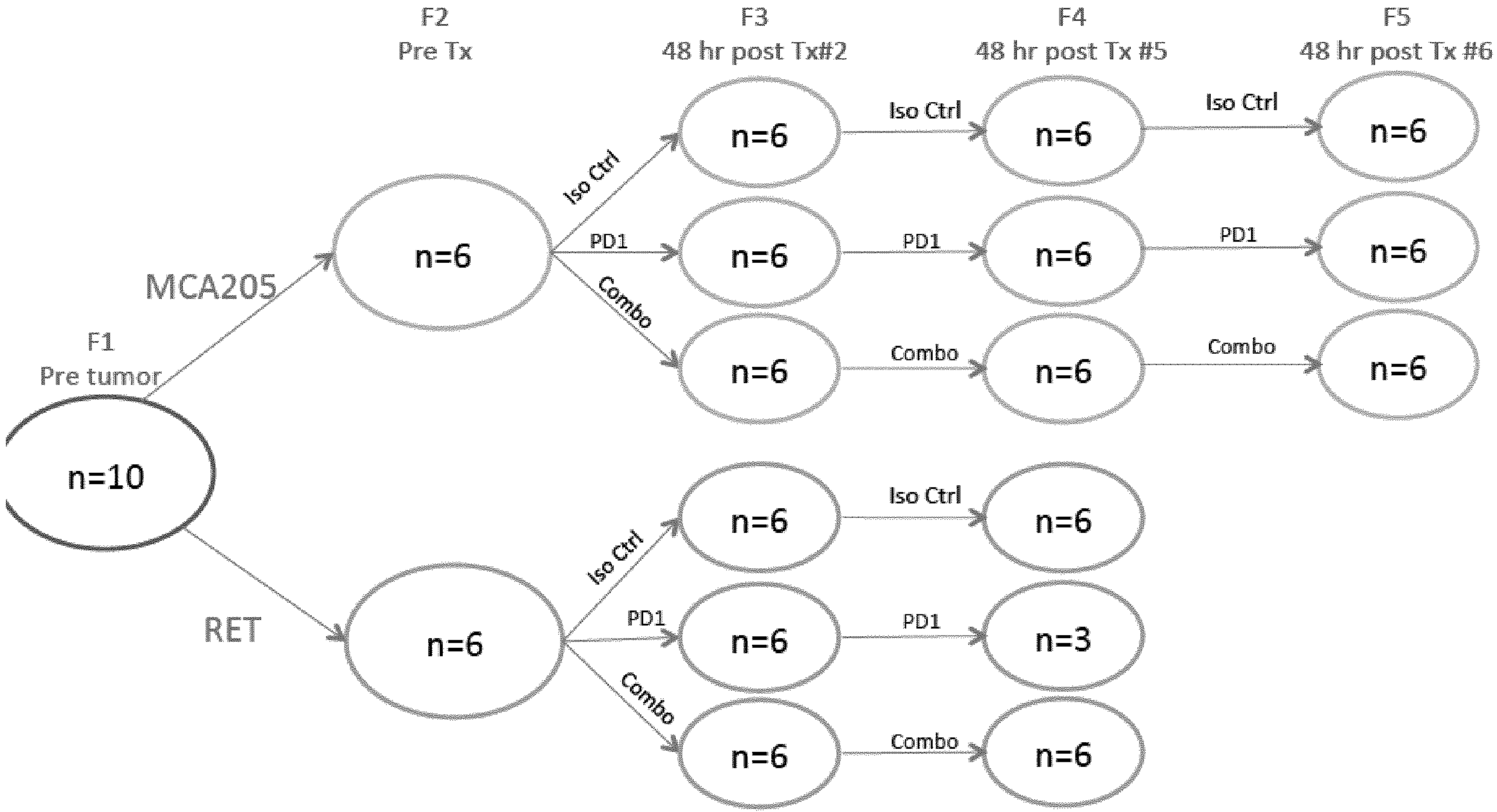


Figure 46

MCA

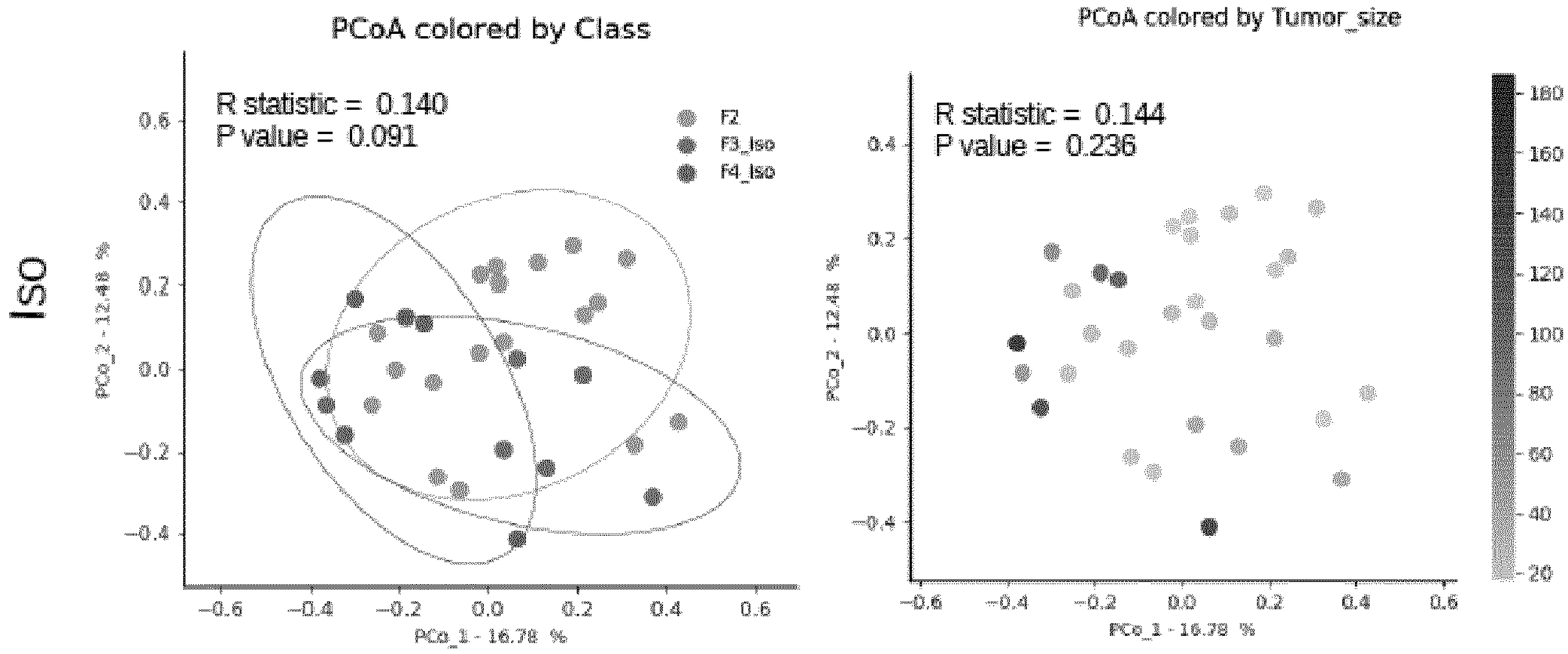


Figure 47

RET

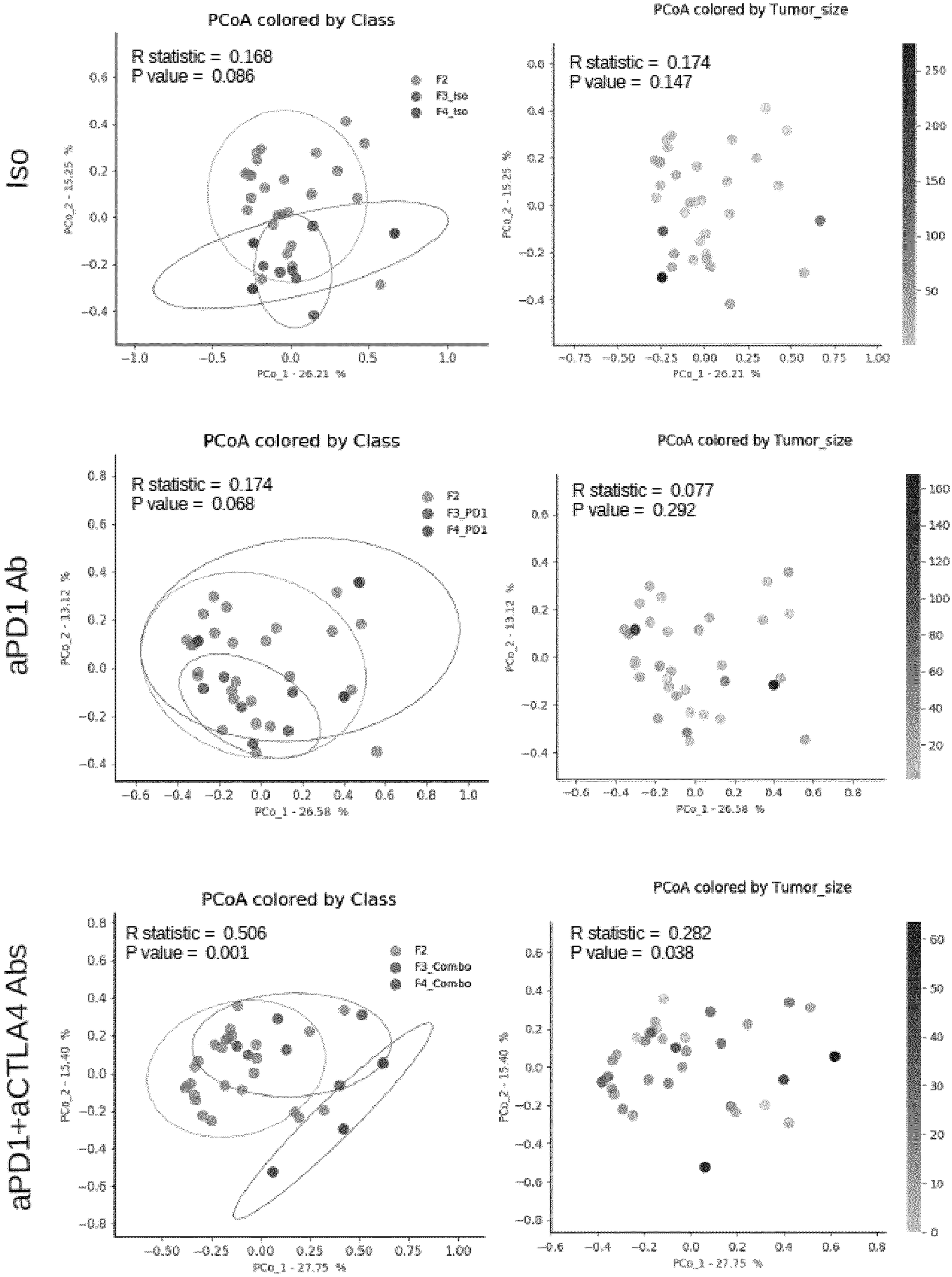
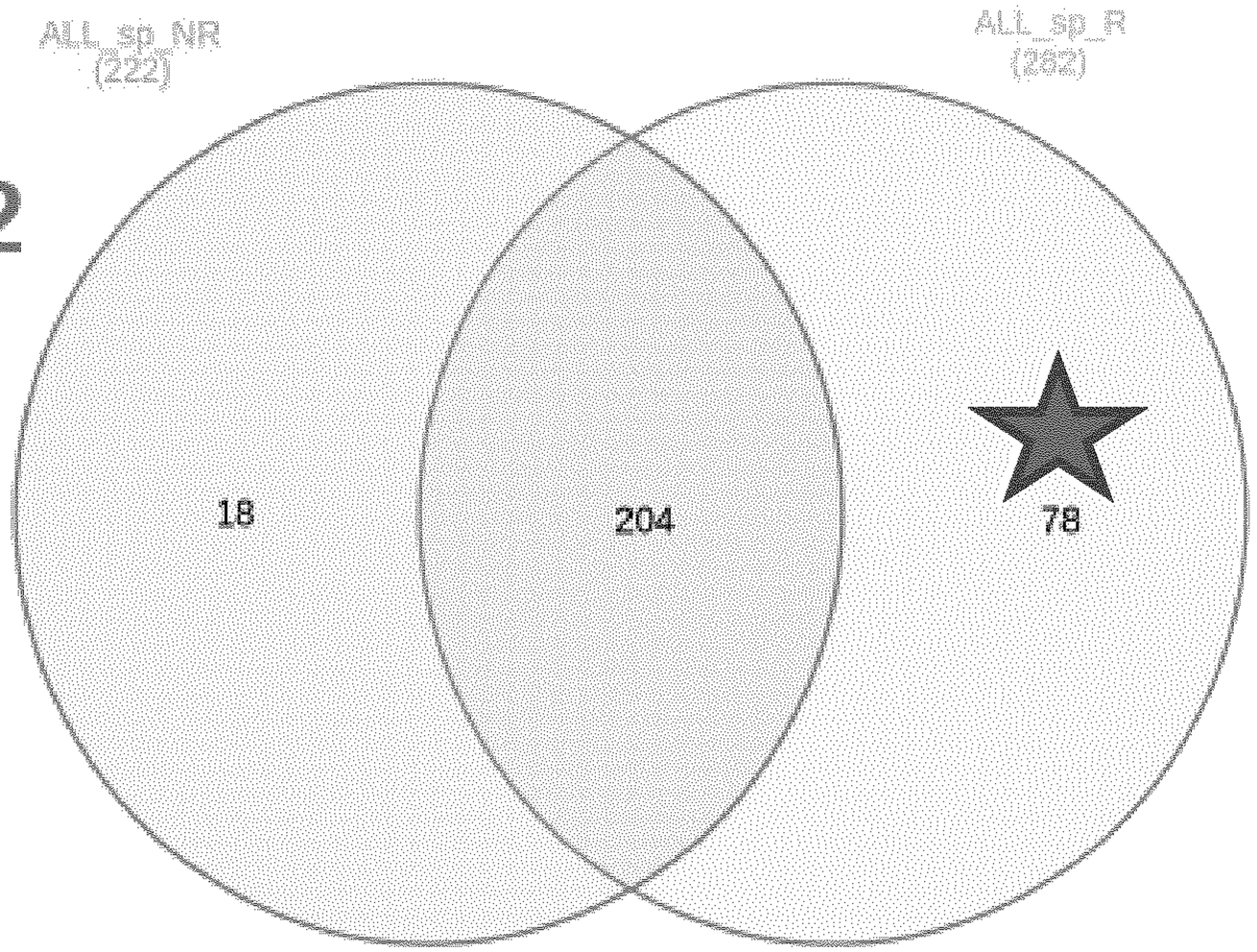


Figure 48

F2



Species in common: 204

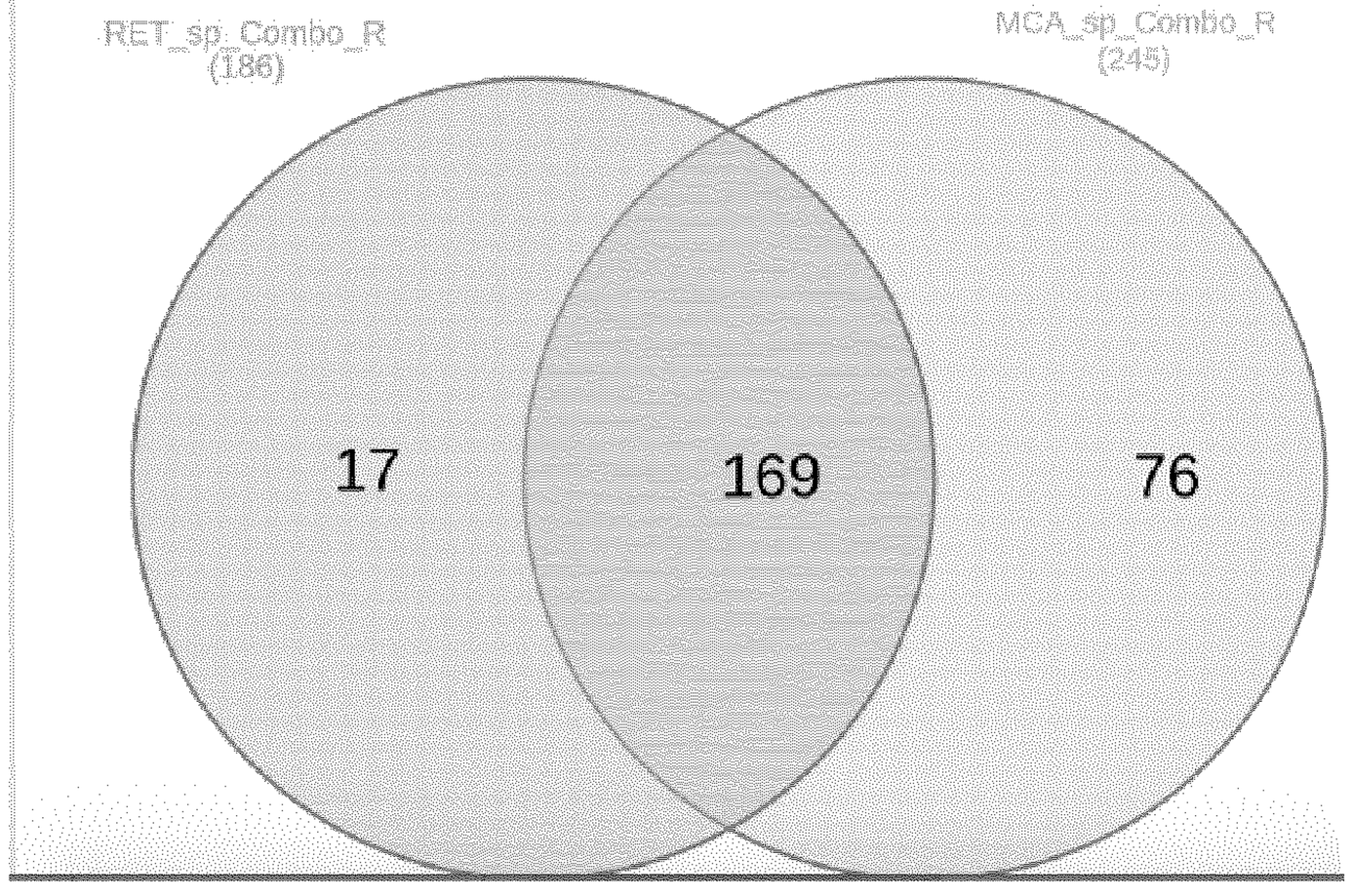
SPECIES ONLY IN **R** (n=78):

Acidovorax_radicis
Agathobaculum_desmolans
Alicyclobacillus_pomorum
Alistipes_onderdonkii
Alloprevotella_rava
Anaerobranca_gottschalkii
Anaeroplasma_bactoclasticum
Anoxynatronum_sibiricum
Bacillus_deserti
Bacteroides_finegoldii
Bacteroides_intestinalis
Bacteroides_mediterraneensis
Bifidobacterium_animalis
Blautia_faecis
Blautia_marasmi
Blautia_schinkii
Brassicibacter_thermophilus
Brevundimonas_albigilva
Clostridium_amygdalinum
Clostridium_cavendishii
Clostridium_cellulosi
Clostridium_cellulovorans
Clostridium_cylindrosporum
Clostridium_fimetarium
Clostridium_hathewayi
Clostridium_hydrogeniformans
Clostridium_perfringens
Clostridium_senegalense
Clostridium_symbiosum
Clostridium_xylanovorans
Comamonas_piscis
Cryptosporangium_cibodasense
Desulfitobacterium_hafniense
Dielma_fastidiosa
Eisenbergiella_tayi
Ethanoligenens_harbinense
Eubacterium_contortum
Eubacterium_tortuosum
Faecalibacterium_prausnitzii
Faecalicoccus_acidiformans
Fusicatenibacter_saccharivorans
Hungatella_effluvii
Jeotgalicoccus_nanhaiensis
Lactobacillus_amylolyticus
Lactobacillus_antri
Lactobacillus_apodemi
Lactobacillus_brantae
Lactobacillus_mucosae
Lactobacillus_salivarius
Lactobacillus_suebicus
Lactobacillus_tucceti
Mediterranea_massiliensis
Meiothermus_ruber
Mesorhizobium_australicum
Mordavella_massiliensis
Muricomes_intestini
Paenibacillus_curdlanolyticus
Parapedobacter_composti
Paraprevotella_clara
Porphyromonas_gulae
Prevotella_baroniae
Prevotella_copri
Prevotella_loescheii
Prevotella_oralis
Prevotella_paludivivens
Rhizobium_etli
Rhizobium_straminoryzae
Rothia_mucilaginosa
Ruminococcus_lactaris
Saccharofermentans_acetigenes
Spiroplasma_velocicrescens
Staphylococcus_cohnii
Streptococcus_dentisani
Streptococcus_salivarius
Syntrophococcus_sucromutans
Thermanaerovibrio_velox

Figure 49

F2 [RET_sp_Combo_R] and [MCA_sp_Combo_R]:

RET	MCA
n=8	n=6



Abyssivirga_alkaniphila
Acetatifactor_muris
Acetivibrio_cellulolyticus
Acetivibrio_ethanolgignens
Acholeplasma_vituli
Achromobacter_deleyi
Acidovorax_radicis
Adlercreutzia_equolifaciens
Akkermansia_muciniphila
Alistipes_indistinctus
Alistipes_obesi
Alistipes_putredinis
Alistipes_senegalensis
Alistipes_timonensis
Alkalibacter_saccharofermentans
Alkalibaculum_bacchi
Allobaculum_stercoricanis
Anaerobacterium_chartisolvens
Anaerocolumna_cellulosilytica
Anaerosporobacter_mobilis
Anaerotaenia_torta
Anaerotruncus_colihominis
Anaerotruncus_rubiinfantis
Anaerovorax_odorimutans
Bacteroides_acidifaciens
Bacteroides_caecimuris
Bacteroides_dorei
Bacteroides_faecichinchillae
Bacteroides_rodentium
Bacteroides_stercorirosoris
Bacteroides_xylanolyticus
Barnesiella_intestinihominis
Beduini_massiliensis
Bifidobacterium_pseudolongum
Blautia_luti
Breznakia_blatticola
Breznakia_pachnodae
Butyricicoccus_pullicaecorum
Butyrivibrio_crossotus
Catabacter_hongkongensis
Erysipelatoclostridium_ramosum
Erysipelothrix_larvae
Escherichia_fergusonii
Eubacterium_coprostanoligenes
Eubacterium_dolichum
Eubacterium_ruminantium
Eubacterium_siraeum
Eubacterium_tortuosum
Eubacterium_ventriosum
Faecalibaculum_rodentium
Flavimarina_pacifica
Flavonifractor_plautii
Flintibacter_butyricus
Gordonibacter_faecihominis
Gracilibacter_thermotolerans
Harryflintia_acetispora
Holdemania_massiliensis
Hydrogenoanaerobacterium_saccharovorans
Ihubacter_massiliensis
Intestinimonas_butyriciproducens
Irregularibacter_muris
Lachnoclostridium_pacaense
Lactobacillus_animalis
Lactobacillus_faecis
Lactobacillus_gasseri
Lactobacillus_hominis
Lactobacillus_intestinalis
Lactobacillus_johnsonii
Lactobacillus_reuteri
Lactobacillus_rogosae
Lactobacillus_taiwanensis
Lawsonia_intracellularis
Longibaculum_muris
Marvinbryantia_formatexigens
Millionella_massiliensis
Mucispirillum_schaedleri
Muribaculum_intestinale
Murimonas_intestini
Natranaerovirga_pectinivora

Figure 50