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Longitudinal gut microbiome changes in immune checkpoint blockade-treated advanced melanoma

In the format provided by the authors and unedited

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Supplementary figures

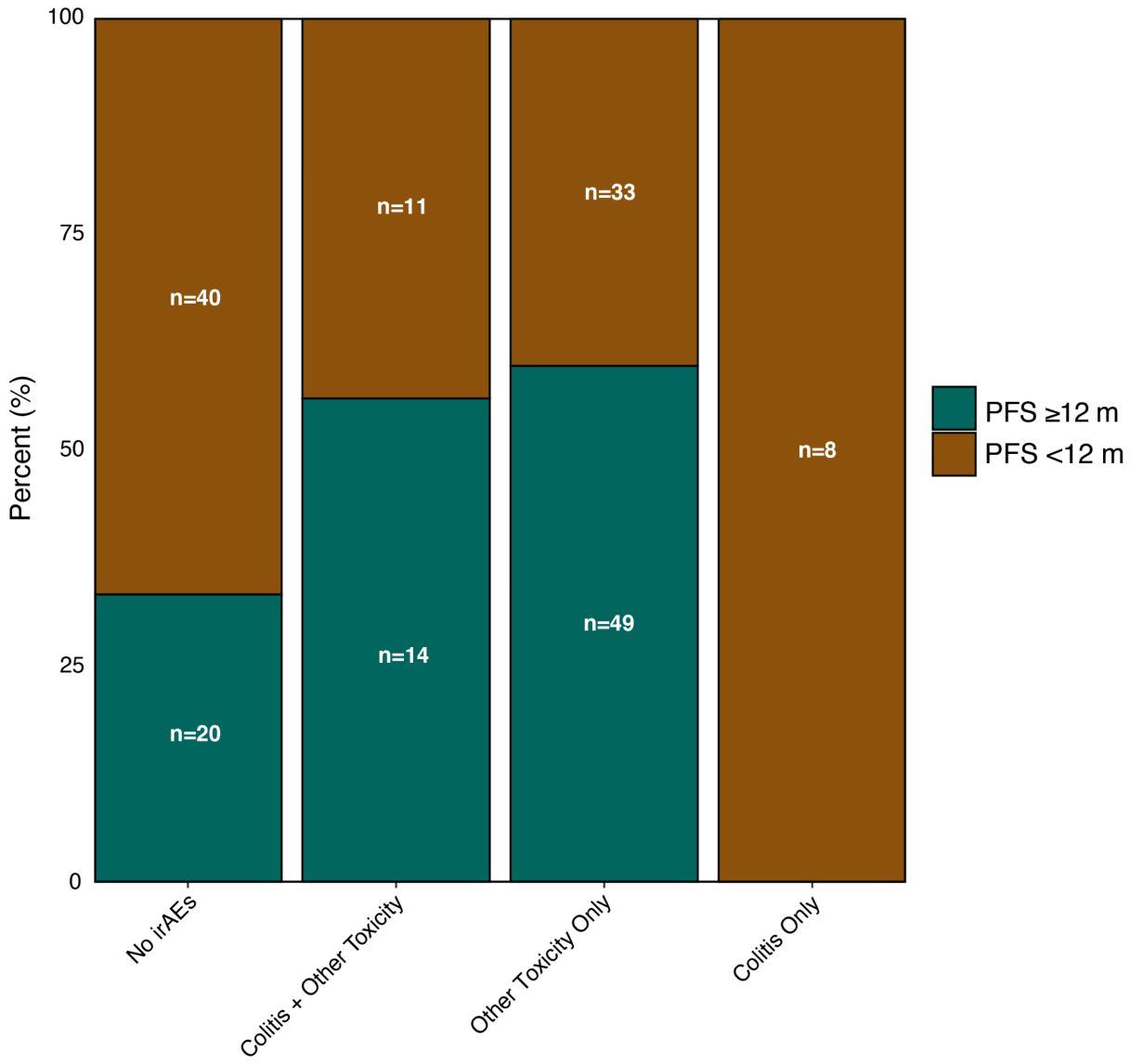
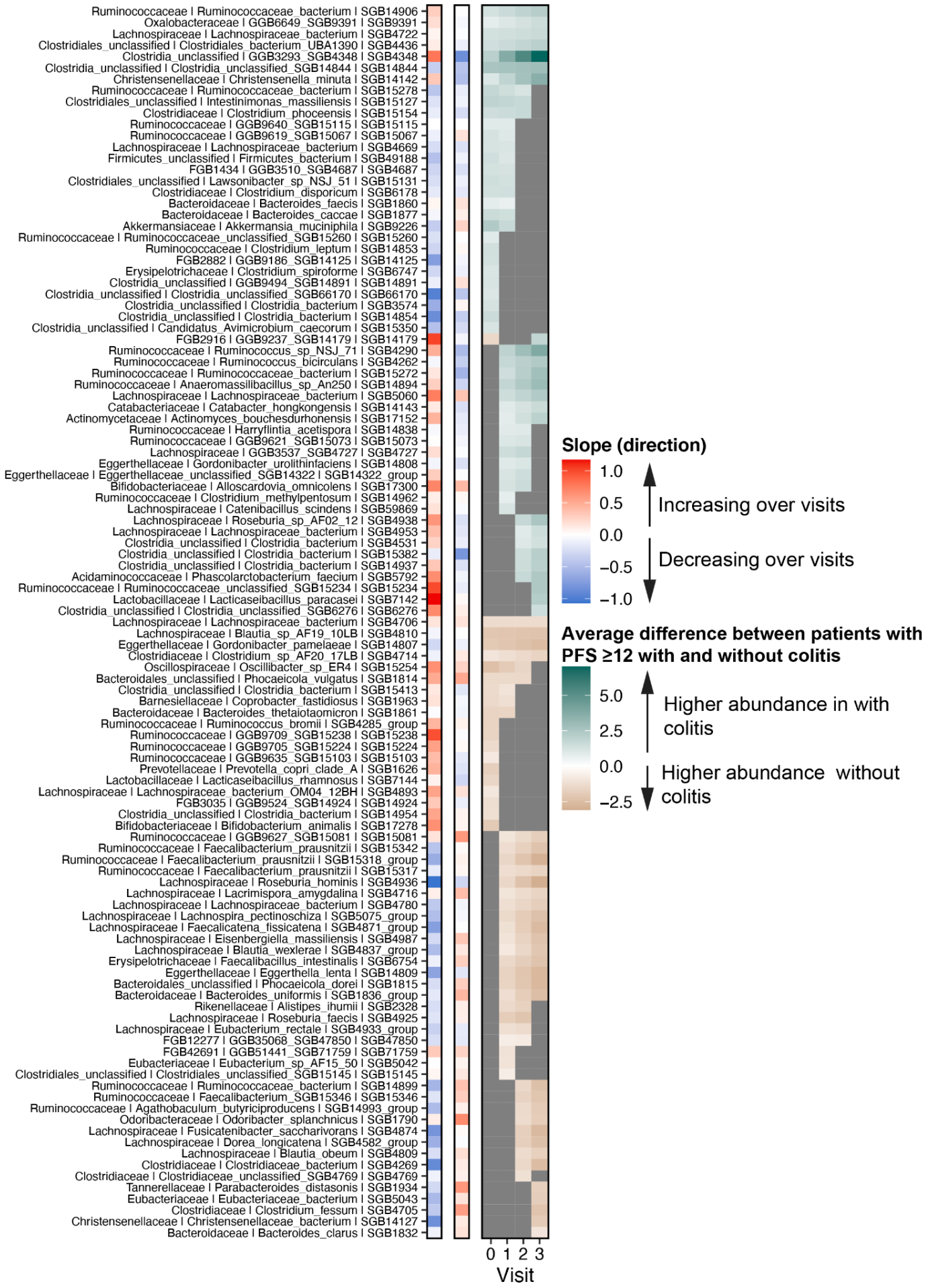


Figure S1. Relationship between PFS12 and irAEs. Mosaic plot for PFS12 and irAEs (separated into colitis and "other toxicity"). The mosaic plot shows how many patients with PFS≥12 and PFS<12 months did not develop any irAEs, how many developed both colitis and other toxicities, how many developed other toxicities but no colitis, and how many patients developed colitis only.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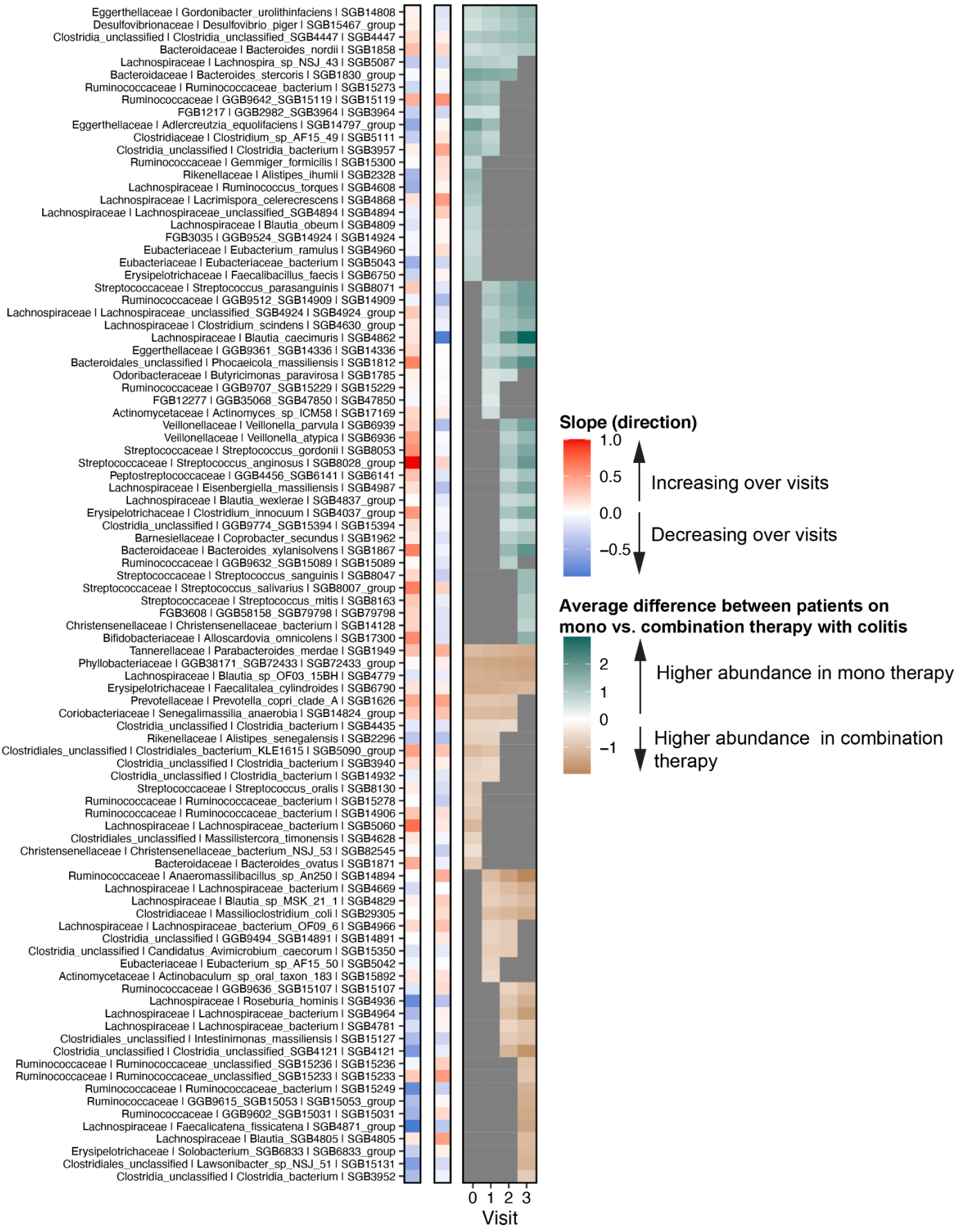
Bacteroidaceae | Bacteroides_clarus | SGB1832
0 1 2 3
Visit
Slope (direction)
1.0
0.5
0.0
−0.5
−1.0
Increasing over visits
Decreasing over visits
Average difference between patients with PFS ≥12 with and without colitis
5.0
2.5
0.0
−2.5
Higher abundance in with colitis
Higher abundance without colitis

Figure S2. Patients with PFS≥12 with and without colitis. Panel (A) shows, for each microbial SGB listed, its slopes in patients with PFS≥12 months with and without colitis, respectively. Red and blue colors indicate whether the focal SGB is increasing or decreasing in its abundance over study visits, respectively. It then shows the average difference between patients with PFS≥12 months with and without colitis across the different study visits. Non-gray cells in the heatmap correspond to the focal SGB's log-fold change in abundance between patients with PFS≥12 months with and without colitis, respectively. Teal cells correspond to study visits for which the abundance of the focal SGB is higher in patients with PFS≥12 months with colitis than in patients with PFS≥12 months without colitis, and vice versa for brown cells (at 90% BCL). Gray cells denote differences between patients with PFS≥12 months with and without colitis whose 90% CI overlapped with zero.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Eubacteriaceae | Eubacterium_ramulus | SGB4960
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Erysipelotrichaceae | Faecalibacillus_faecis | SGB6750
Streptococcaceae | Streptococcus_parasanguinis | SGB8071
Ruminococcaceae | GGB9512_SGB14909 | SGB14909
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Lachnospiraceae | Lachnospiraceae_bacterium | SGB4669
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Ruminococcaceae | GGB9615_SGB15053 | SGB15053_group
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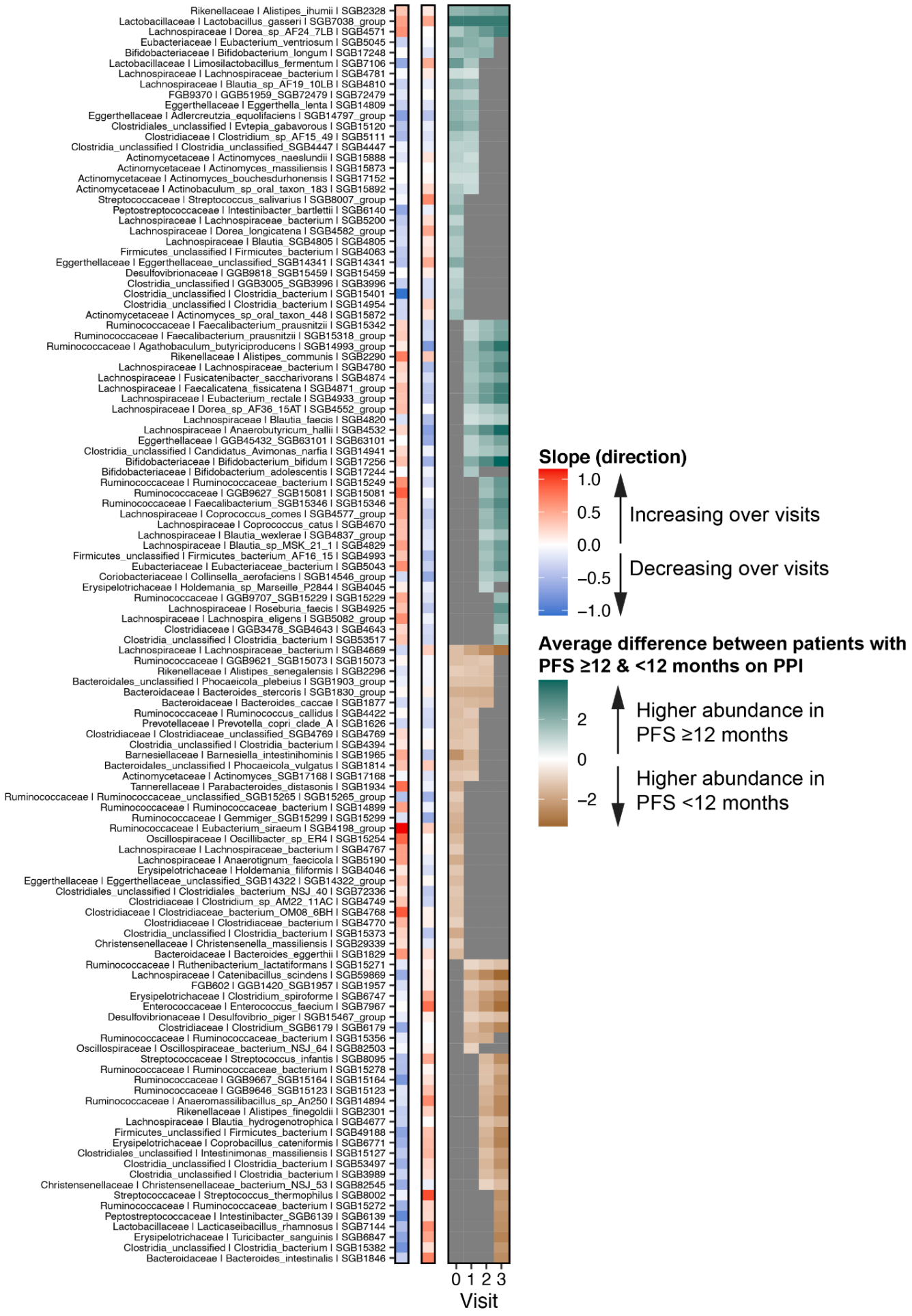
Lachnospiraceae | Blautia_SGB4805 | SGB4805
Erysipelotrichaceae | Solobacterium_SGB6833 | SGB6833_group
Clostridiales_unclassified | Lawsonibacter_sp_NSJ_51 | SGB15131
Clostridia_unclassified | Clostridia_bacterium | SGB3952
0 1 2 3
Visit
Slope (direction)
1.0
0.5
0.0
−0.5
Increasing over visits
Decreasing over visits
Average difference between patients on mono vs. combination therapy with colitis
2
1
0
−1
Higher abundance in mono therapy
Higher abundance in combination therapy

Figure S3. Patients on combination therapy and monotherapy who developed colitis. The figure shows, for each microbial SGB listed, its slopes in patients who developed colitis on combination therapy and monotherapy, respectively. Red and blue colors indicate whether the focal SGB is increasing or decreasing in its abundance over study visits, respectively. It then shows the average difference between patients on combination therapy and monotherapy across the different study visits. Non-gray cells in the heatmap correspond to the focal SGB's log-fold change in abundance between patients on combination and monotherapy, respectively. Teal cells correspond to study visits for which the abundance of the focal SGB is higher in patients who developed colitis on combination therapy compared to those who developed colitis on monotherapy, and vice versa for brown cells (at 90% BCL). Gray cells denote differences between patients with and without colitis whose 90% CI overlapped with zero.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Enterococcaceae | Enterococcus_faecium | SGB7967
Desulfovibrionaceae | Desulfovibrio_piger | SGB15467_group
Clostridiaceae | Clostridium_SGB6179 | SGB6179
Ruminococcaceae | Ruminococcaceae_bacterium | SGB15356
Oscillospiraceae | Oscillospiraceae_bacterium_NSJ_64 | SGB82503
Streptococcaceae | Streptococcus_infantis | SGB8095
Ruminococcaceae | Ruminococcaceae_bacterium | SGB15278
Ruminococcaceae | GGB9667_SGB15164 | SGB15164
Ruminococcaceae | GGB9646_SGB15123 | SGB15123
Ruminococcaceae | Anaeromassilibacillus_sp_An250 | SGB14894
Rikenellaceae | Alistipes_finegoldii | SGB2301
Lachnospiraceae | Blautia_hydrogenotrophica | SGB4677
Firmicutes_unclassified | Firmicutes_bacterium | SGB49188
Erysipelotrichaceae | Coprobacillus_cateniformis | SGB6771
Clostridiales_unclassified | Intestinimonas_massiliensis | SGB15127
Clostridia_unclassified | Clostridia_bacterium | SGB53497
Clostridia_unclassified | Clostridia_bacterium | SGB3989
Christensenellaceae | Christensenellaceae_bacterium_NSJ_53 | SGB82545
Streptococcaceae | Streptococcus_thermophilus | SGB8002
Ruminococcaceae | Ruminococcaceae_bacterium | SGB15272
Peptostreptococcaceae | Intestinibacter_SGB6139 | SGB6139
Lactobacillaceae | Lacticaseibacillus_rhamnosus | SGB7144
Erysipelotrichaceae | Turicibacter_sanguinis | SGB6847
Clostridia_unclassified | Clostridia_bacterium | SGB15382
Bacteroidaceae | Bacteroides_intestinalis | SGB1846
0 1 2 3
Visit
Slope (direction)
1.0
0.5
0.0
−0.5
−1.0
Increasing over visits
Decreasing over visits
Average difference between patients with PFS ≥12 & <12 months on PPI
2
0
−2
Higher abundance in PFS ≥12 months
Higher abundance in PFS <12 months

Figure S4. **Patients with PFS≥12 and PFS<12 months who used PPIs**. The figure shows, for each microbial SGB listed, its slopes in patients with PFS≥12 and PFS<12 months who used PPIs, respectively. Red and blue colors indicate whether the focal SGB is increasing or decreasing in its abundance over study visits, respectively. It then shows the average difference between patients with PFS≥12 and PFS<12 months across the different study visits. Non-gray cells in the heatmap correspond to the focal SGB's log-fold change in abundance between patients with PFS≥12 and PFS<12 months, respectively. Teal cells correspond to study visits for which the abundance of the focal SGB is higher in patients with PFS≥12 than with PFS<12 months, and vice versa for brown cells (at 90% BCL). Gray cells denote differences between patients who used and did not use PPIs whose 90% CI overlapped with zero.

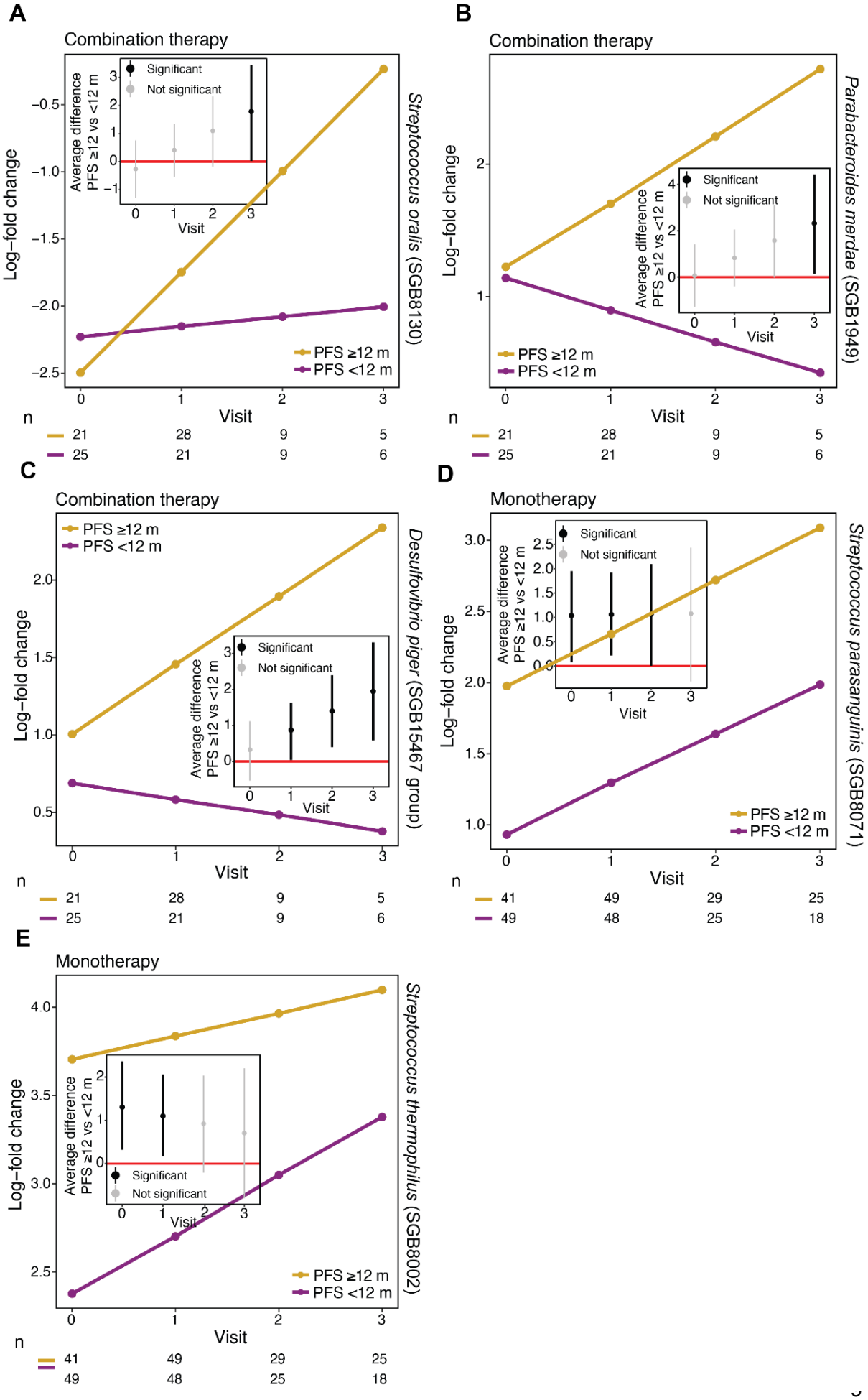
A
Combination therapy
Log−fold change
Visit
Average difference PFS ≥12 vs <12 m
Significant
Not significant
PFS ≥12 m
PFS <12 m
Streptococcus oralis (SGB8130)
n
21 28 9 5
25 21 9 6
B
Combination therapy
Parabacteroides merdae (SGB1949)
21 28 9 5
25 21 9 6
C
Combination therapy
Desulfovibrio piger (SGB15467 group)
21 28 9 5
25 21 9 6
D
Monotherapy
Streptococcus parasanguinis (SGB8071)
41 49 29 25
49 48 25 18
E
Monotherapy
Streptococcus thermophilus (SGB8002)
41 49 29 25
49 48 25 18

Figure S5. Pro-inflammatory SGBs increase in patients with PFS≥12 months. Panels (A-E) show five different “dynamical scenarios” exemplified by different “pro-inflammatory” SGBs increasing in patients with PFS≥12 months during ICB. The teal and brown lines correspond to regression slopes across the study visits for patients with PFS≥12 and PFS<12 months, respectively. Panels (A-C) display SGBs under combination therapy, while panels (D-E) show SGBs under monotherapy. The y-axis shows the clr log-ratio value for each study visit (x-axis). The corresponding inset plots show the average difference between patients with PFS≥12 and PFS<12 months at each study visit, including the 90% credible interval; if this does not cross the red zero line, then we deem the focal SGB differentially abundant in the focal study visit.

Supplementary methods

Patients with PFS≥12 months vs. patients with PFS<12 months

The below reference grid shows all combinations of the levels of W_{1-3} for patients with PFS<12 months ($Z = 0$) and patients with PFS≥12 months ($Z = 1$), respectively. The 5th column shows, for each combination, the non-zero coefficients for PFS<12 (A-H) and PFS≥12 (I-P), respectively.

	W_1	W_2	W_3	Patients with PFS<12 months ($Z = 0$)
A	0	0	0	$\beta_0 + \beta_1$
B	1	0	0	$\beta_0 + \beta_1 + \beta_4 + \beta_5$
C	0	1	0	$\beta_0 + \beta_1 + \beta_8 + \beta_9$
D	0	0	1	$\beta_0 + \beta_1 + \beta_{12} + \beta_{13}$
E	1	1	0	$\beta_0 + \beta_1 + \beta_4 + \beta_5 + \beta_8 + \beta_9$
F	0	1	1	$\beta_0 + \beta_1 + \beta_8 + \beta_9 + \beta_{12} + \beta_{13}$
G	1	0	1	$\beta_0 + \beta_1 + \beta_4 + \beta_5 + \beta_{12} + \beta_{13}$
H	1	1	1	$\beta_0 + \beta_1 + \beta_4 + \beta_5 + \beta_8 + \beta_9 + \beta_{12} + \beta_{13}$
	W_1	W_2	W_3	Patients with PFS≥12 months ($Z = 1$)
I	0	0	0	$\beta_0 + \beta_1 + \beta_2 + \beta_3$
J	1	0	0	$\beta_0 + \beta_1 + \beta_2 + \beta_3 + \beta_4 + \beta_5 + \beta_6 + \beta_7$
K	0	1	0	$\beta_0 + \beta_1 + \beta_2 + \beta_3 + \beta_8 + \beta_9 + \beta_{10} + \beta_{11}$
L	0	0	1	$\beta_0 + \beta_1 + \beta_2 + \beta_3 + \beta_{12} + \beta_{13} + \beta_{14} + \beta_{15}$
M	1	1	0	$\beta_0 + \beta_1 + \beta_2 + \beta_3 + \beta_4 + \beta_5 + \beta_6 + \beta_7 + \beta_8 + \beta_9 + \beta_{10} + \beta_{11}$
N	0	1	1	$\beta_0 + \beta_1 + \beta_2 + \beta_3 + \beta_8 + \beta_9 + \beta_{10} + \beta_{11} + \beta_{12} + \beta_{13} + \beta_{14} + \beta_{15}$
O	1	0	1	$\beta_0 + \beta_1 + \beta_2 + \beta_3 + \beta_4 + \beta_5 + \beta_6 + \beta_7 + \beta_{12} + \beta_{13} + \beta_{14} + \beta_{15}$
P	1	1	1	$\beta_0 + \beta_1 + \beta_2 + \beta_3 + \beta_4 + \beta_5 + \beta_6 + \beta_7 + \beta_8 + \beta_9 + \beta_{10} + \beta_{11} + \beta_{12} + \beta_{13} + \beta_{14} + \beta_{15}$

With this reference grid established, we can use the estimated coefficients to compute the marginal mean for patients with PFS≥12 vs. PFS<12 respectively.

$$\widehat{PFS<12} = \frac{A+B+C+D+E+F+G+H}{8}$$
$$= \underbrace{\beta_0 + 0.5\big(\beta_4+\beta_8+\beta_{12}\big)}_{\text{intercepts}} + \underbrace{\big(\beta_1 + 0.5\big(\beta_5+\beta_9+\beta_{13}\big)\big)}_{\text{slopes}} X$$

$$\widehat{PFS\geq 12} = \frac{I+J+K+L+M+N+O+P}{8}$$
$$\underbrace{\beta_0+\beta_2+0.5\Big(\beta_4+\beta_6+\beta_8+\beta_{10}+\beta_{12}+\beta_{14}\Big)}_{\text{intercepts}} + \underbrace{\Big(\beta_1+\beta_3+0.5\Big(\beta_5+\beta_7+\beta_9+\beta_{11}+\beta_{13}+\beta_{15}\Big)\Big)}_{\text{slopes}} X$$

Then, finding the difference between the marginal averages for patients with PFS≥12 vs. PFS<12 months, we simply subtract one from the other

$$\widehat{PFS\geq 12} - \widehat{PFS<12} = \underbrace{\beta_2 + 0.5\big(\beta_6+\beta_{10}+\beta_{14}\big)}_{\text{intercepts}} + \underbrace{\big(\beta_3 + 0.5\big(\beta_7+\beta_{11}+\beta_{15}\big)\big)}_{\text{slopes}} X$$

Colitis vs. no colitis

The below reference grid shows all combinations of the levels of Z , W_1 and W_3 for "no colitis" ($W_2 = 0$) and "colitis" ($W_2 = 1$), respectively. The 5th column shows, for each combination, the non-zero coefficients for "no colitis" (A-H) and "colitis" (I-P), respectively.

	Z	W_1	W_3	No colitis ($W_2 = 0$)
A	0	0	0	$\beta_0 + \beta_1$
B	1	0	0	$\beta_0 + \beta_1 + \beta_2 + \beta_3$
C	0	1	0	$\beta_0 + \beta_1 + \beta_4 + \beta_5$
D	0	0	1	$\beta_0 + \beta_1 + \beta_{12} + \beta_{13}$
E	1	1	0	$\beta_0 + \beta_1 + \beta_2 + \beta_3 + \beta_4 + \beta_5 + \beta_6 + \beta_7$
F	0	1	1	$\beta_0 + \beta_1 + \beta_4 + \beta_5 + \beta_{12} + \beta_{13}$
G	1	0	1	$\beta_0 + \beta_1 + \beta_2 + \beta_3 + \beta_{12} + \beta_{13} + \beta_{14} + \beta_{15}$
H	1	1	1	$\beta_0 + \beta_1 + \beta_2 + \beta_3 + \beta_4 + \beta_5 + \beta_6 + \beta_7 + \beta_{12} + \beta_{13} + \beta_{14} + \beta_{15}$
	Z	W_1	W_3	Colitis ($W_2 = 1$)
I	0	0	0	$\beta_0 + \beta_1 + \beta_8 + \beta_9$
J	1	0	0	$\beta_0 + \beta_1 + \beta_2 + \beta_3 + \beta_8 + \beta_9 + \beta_{10} + \beta_{11}$
K	0	1	0	$\beta_0 + \beta_1 + \beta_4 + \beta_5 + \beta_8 + \beta_9$
L	0	0	1	$\beta_0 + \beta_1 + \beta_8 + \beta_9 + \beta_{12} + \beta_{13}$

M	1	1	0	$\beta_0+\beta_1+\beta_2+\beta_3+\beta_4+\beta_5+\beta_6+\beta_7+\beta_8+\beta_9+\beta_{10}+\beta_{11}$
N	0	1	1	$\beta_0+\beta_1+\beta_4+\beta_5+\beta_8+\beta_9+\beta_{12}+\beta_{13}$
O	1	0	1	$\beta_0+\beta_1+\beta_2+\beta_3+\beta_8+\beta_9+\beta_{10}+\beta_{11}+\beta_{12}+\beta_{13}+\beta_{14}+\beta_{15}$
P	1	1	1	$\beta_0+\beta_1+\beta_2+\beta_3+\beta_4+\beta_5+\beta_6+\beta_7+\beta_8+\beta_9+\beta_{10}+\beta_{11}+\beta_{12}+\beta_{13}+\beta_{14}+\beta_{15}$

$$\widehat{\text{No colitis}} = \frac{A+B+C+D+E+F+G+H}{8}$$
$$= \underbrace{\beta_0+0.5(\beta_2+\beta_4+\beta_{12})+0.25(\beta_6+\beta_{14})}_{\text{intercepts}} + \underbrace{(\beta_1+0.5(\beta_3+\beta_5+\beta_{13})+0.25(\beta_7+\beta_{15}))}_{\text{slopes}}X$$

$$\widehat{\text{Colitis}} = \frac{I+J+K+L+M+N+O+P}{8}$$
$$= \underbrace{\beta_0+\beta_8+0.5(\beta_2+\beta_4+\beta_{10}+\beta_{12})+0.25(\beta_6+\beta_{14})}_{\text{intercepts}} + \underbrace{(\beta_1+\beta_9+0.5(\beta_3+\beta_5+\beta_{11}+\beta_{13})+0.25(\beta_7+\beta_{15}))}_{\text{slopes}}X$$

Then, finding the difference between the marginal averages for patients with and without colitis, we simply subtract one from the other

$$\widehat{\text{Colitis}} - \widehat{\text{No colitis}} = \underbrace{\beta_8+0.5(\beta_{10})}_{\text{intercepts}} + \underbrace{(\beta_9+0.5(\beta_{11}))}_{\text{slopes}}X$$

Patients with PFS≥12 months with and without colitis

The below reference grid shows all combinations of the levels of W_1 and W_3 for patients with PFS≥12 months ($Z=1$) without colitis ($W_2=0$) and patients with PFS≥12 months ($Z=1$) with colitis ($W_2=1$), respectively. The 5th column shows, for each combination, the non-zero coefficients for patients with PFS≥12 months without colitis (A-D) and patients with PFS≥12 months with colitis (E-G), respectively.

	W_1	W_3	Patients with ≥ PFS12 m ($Z=1$) without colitis ($W_2=0$)
A	0	0	$\beta_0+\beta_1+\beta_2+\beta_3$
B	1	0	$\beta_0+\beta_1+\beta_2+\beta_3+\beta_4+\beta_5+\beta_6+\beta_7$
C	0	1	$\beta_0+\beta_1+\beta_2+\beta_3+\beta_{12}+\beta_{13}+\beta_{14}+\beta_{15}$
D	1	1	$\beta_0+\beta_1+\beta_2+\beta_3+\beta_4+\beta_5+\beta_6+\beta_7+\beta_{12}+\beta_{13}+\beta_{14}+\beta_{15}$
	W_1	W_3	Patients with ≥ PFS12 m ($Z=1$) with colitis ($W_2=1$)
E	0	0	$\beta_0+\beta_1+\beta_2+\beta_3+\beta_8+\beta_9+\beta_{10}+\beta_{11}$

F	1	0	$\beta_0 + \beta_1 + \beta_2 + \beta_3 + \beta_4 + \beta_5 + \beta_6 + \beta_7 + \beta_8 + \beta_9 + \beta_{10} + \beta_{11}$
G	0	1	$\beta_0 + \beta_1 + \beta_2 + \beta_3 + \beta_8 + \beta_9 + \beta_{10} + \beta_{11} + \beta_{12} + \beta_{13} + \beta_{14} + \beta_{15}$
H	1	1	$\beta_0 + \beta_1 + \beta_2 + \beta_3 + \beta_4 + \beta_5 + \beta_6 + \beta_7 + \beta_8 + \beta_9 + \beta_{10} + \beta_{11} + \beta_{12} + \beta_{13} + \beta_{14} + \beta_{15}$

$$\widehat{\text{without colitis}} = \frac{A + B + C + D}{4}$$
$$= \underbrace{\beta_0 + \beta_2 + 0.5\big(\beta_4 + \beta_6 + \beta_{12} + \beta_{14}\big)}_{\text{intercepts}} + \underbrace{\big(\beta_1 + \beta_3 + 0.5\big(\beta_5 + \beta_7 + \beta_{13} + \beta_{15}\big)\big)}_{\text{slopes}} X$$

$$\widehat{\text{with colitis}} = \frac{E + F + G + H}{4}$$
$$= \underbrace{\beta_0 + \beta_2 + \beta_8 + \beta_10 + 0.5\big(\beta_4 + \beta_6 + \beta_{12} + \beta_{14}\big)}_{\text{intercepts}} + \underbrace{\big(\beta_1 + \beta_3 + \beta_9 + \beta_{11} + 0.5\big(\beta_5 + \beta_7 + \beta_{13} + \beta_{15}\big)\big)}_{\text{slopes}} X$$

Then, finding the difference between the marginal averages for PFS≥12 months with and without colitis, we simply subtract one from the other

$$\widehat{\text{with colitis}} - \widehat{\text{without colitis}} = \underbrace{\beta_8 + \beta_{10}}_{\text{intercepts}} + \underbrace{\big(\beta_9 + \beta_{11}\big)}_{\text{slopes}} X$$