

15th MADRID
on **Lung** CONGRESS
CANCER
23&24
November 2023

#15CongressGeCP

Microbiome Analysis Predicts Neoadjuvant Treatment Outcomes with Chemo-Immunotherapy in Resectable NSCLC

Roberto Serna Blasco

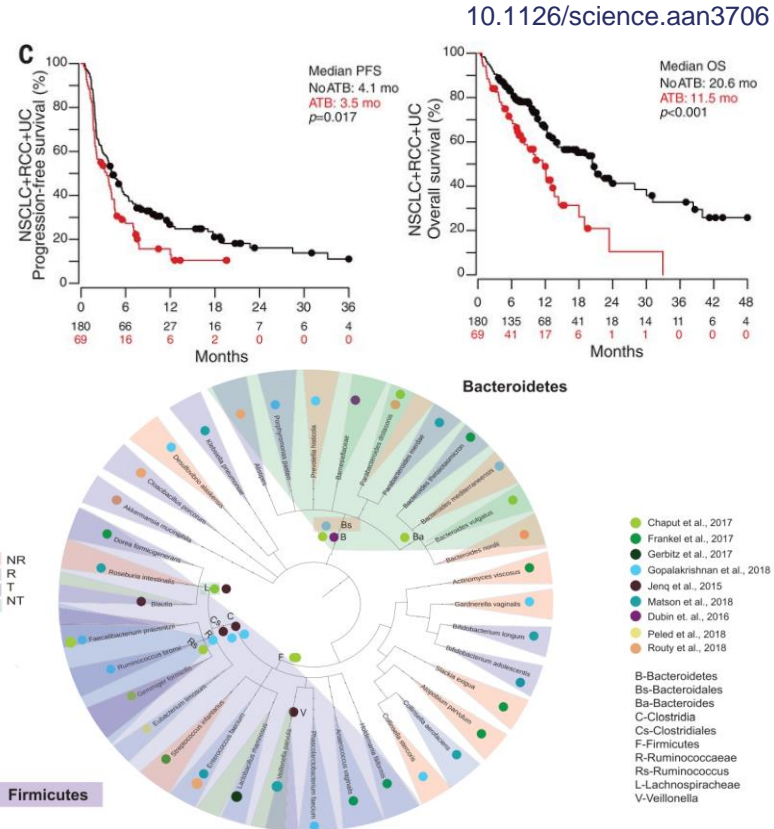
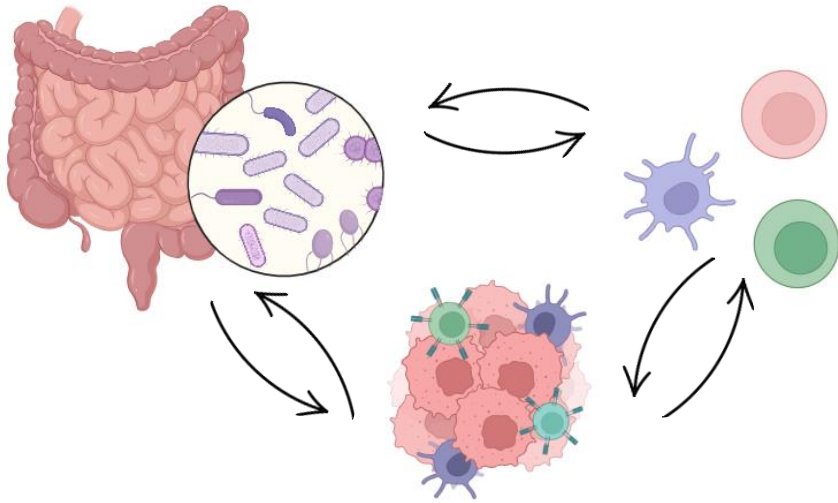
Instituto de Investigación Sanitaria Puerta de Hierro – Segovia de Arana



1. Introducción



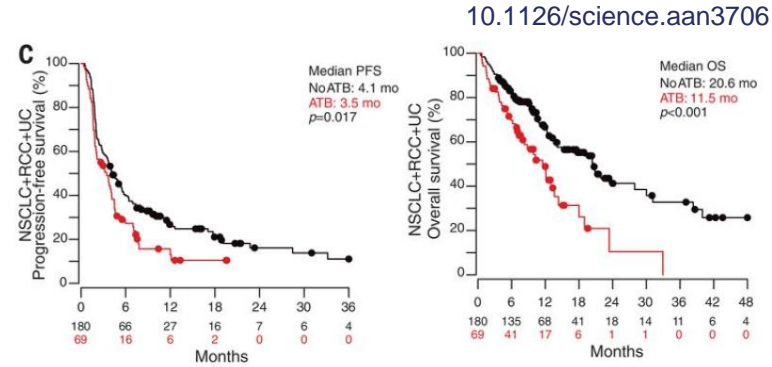
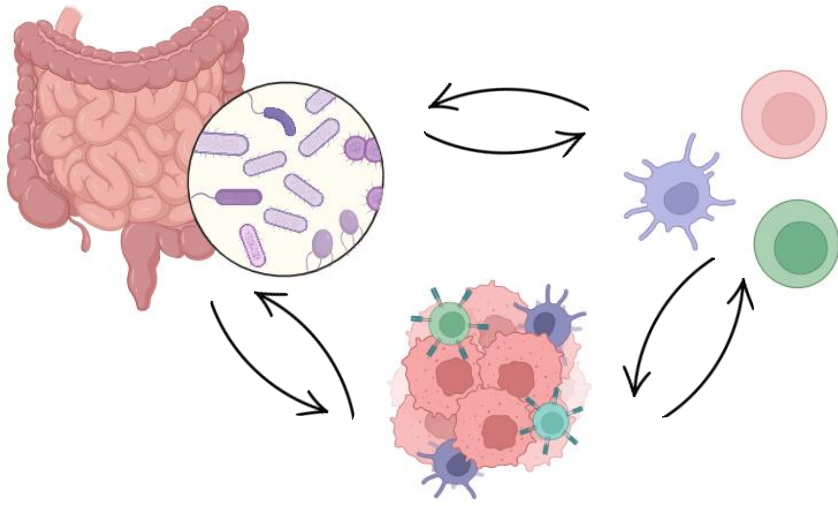
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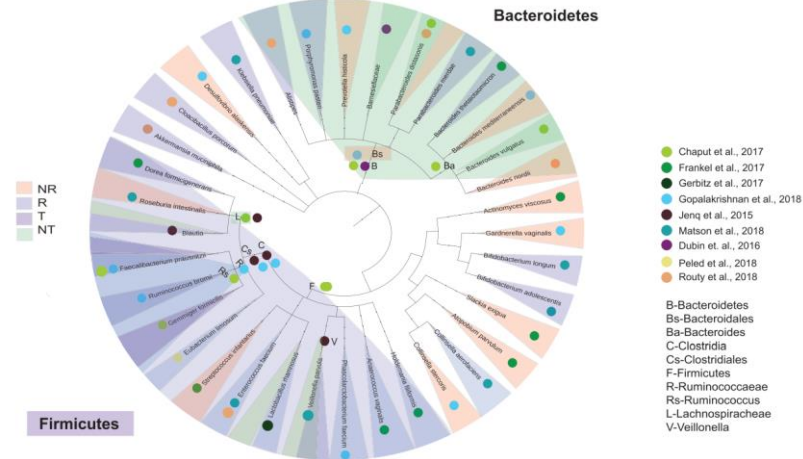
<https://doi.org/10.1016/j.canlet.2019.01.015>



1. Introducción



10.1126/science.aan3706



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REPORT | f | t | in | | | |

Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy

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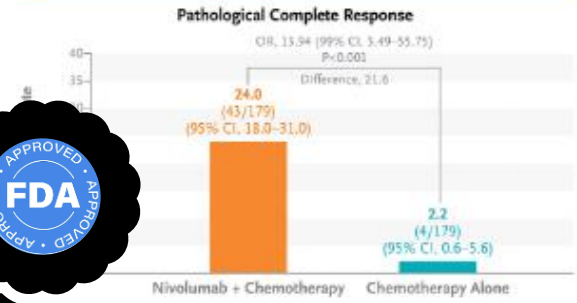
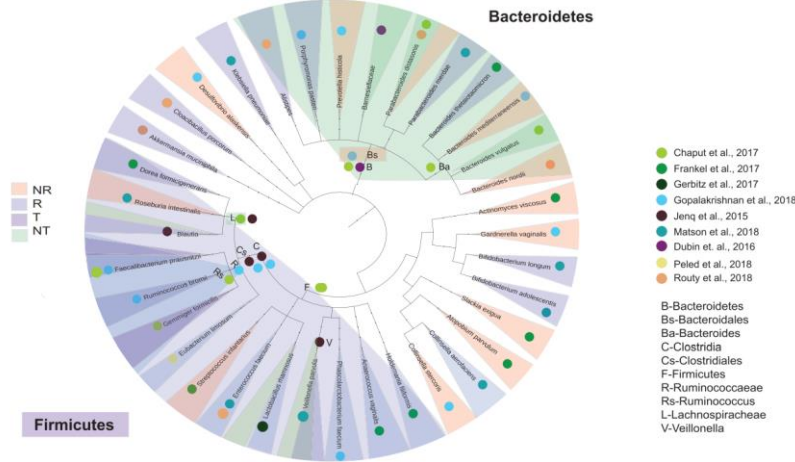
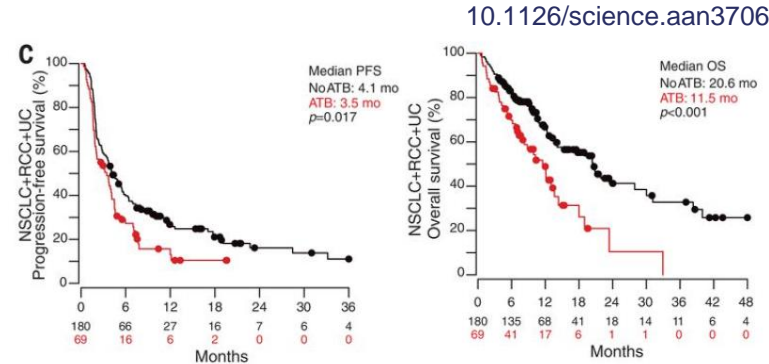
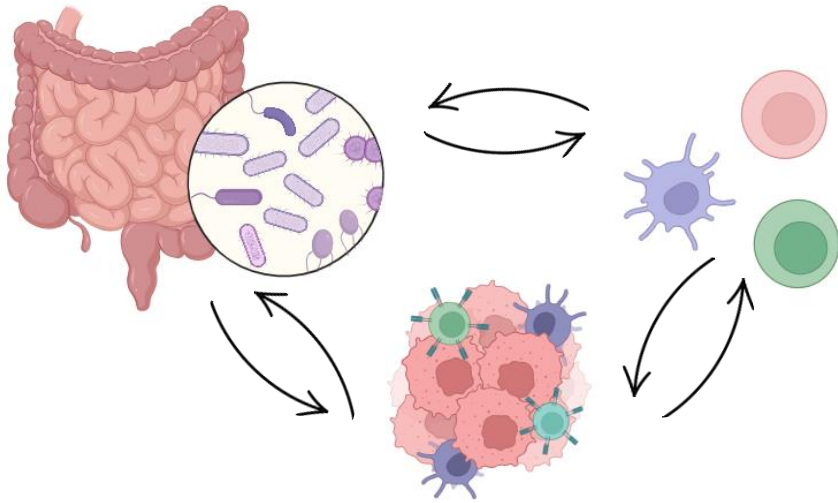
Intestinal *Akkermansia muciniphila* predicts clinical response to PD-1 blockade in patients with advanced non-small-cell lung cancer

nature COMMUNICATIONS | ARTICLE | Received 11 Nov 2015 | Accepted 7 Dec 2015 | Published 2 Feb 2016 | DOI: 10.1038/ncomms10391 | OPEN

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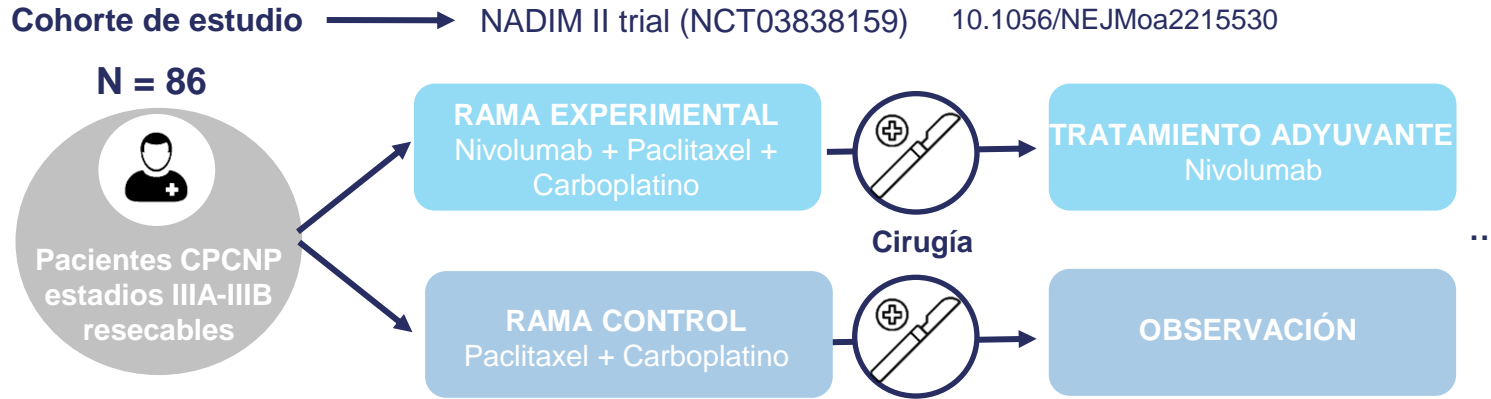
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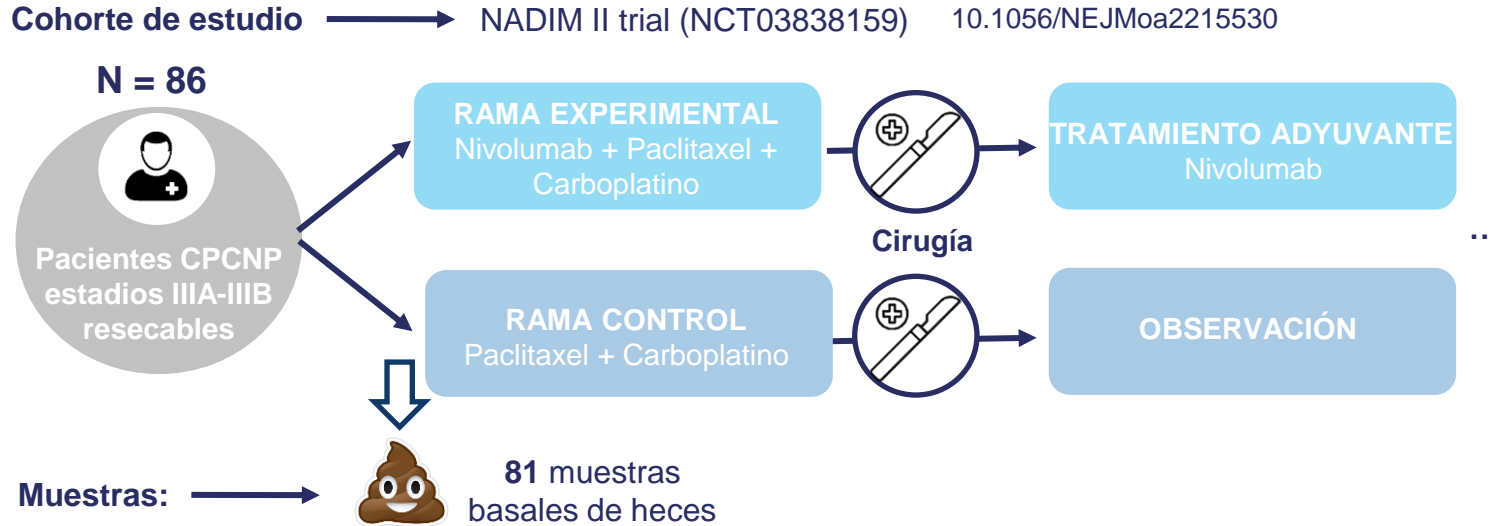
2. Pacientes y metodología

Cohorte de estudio

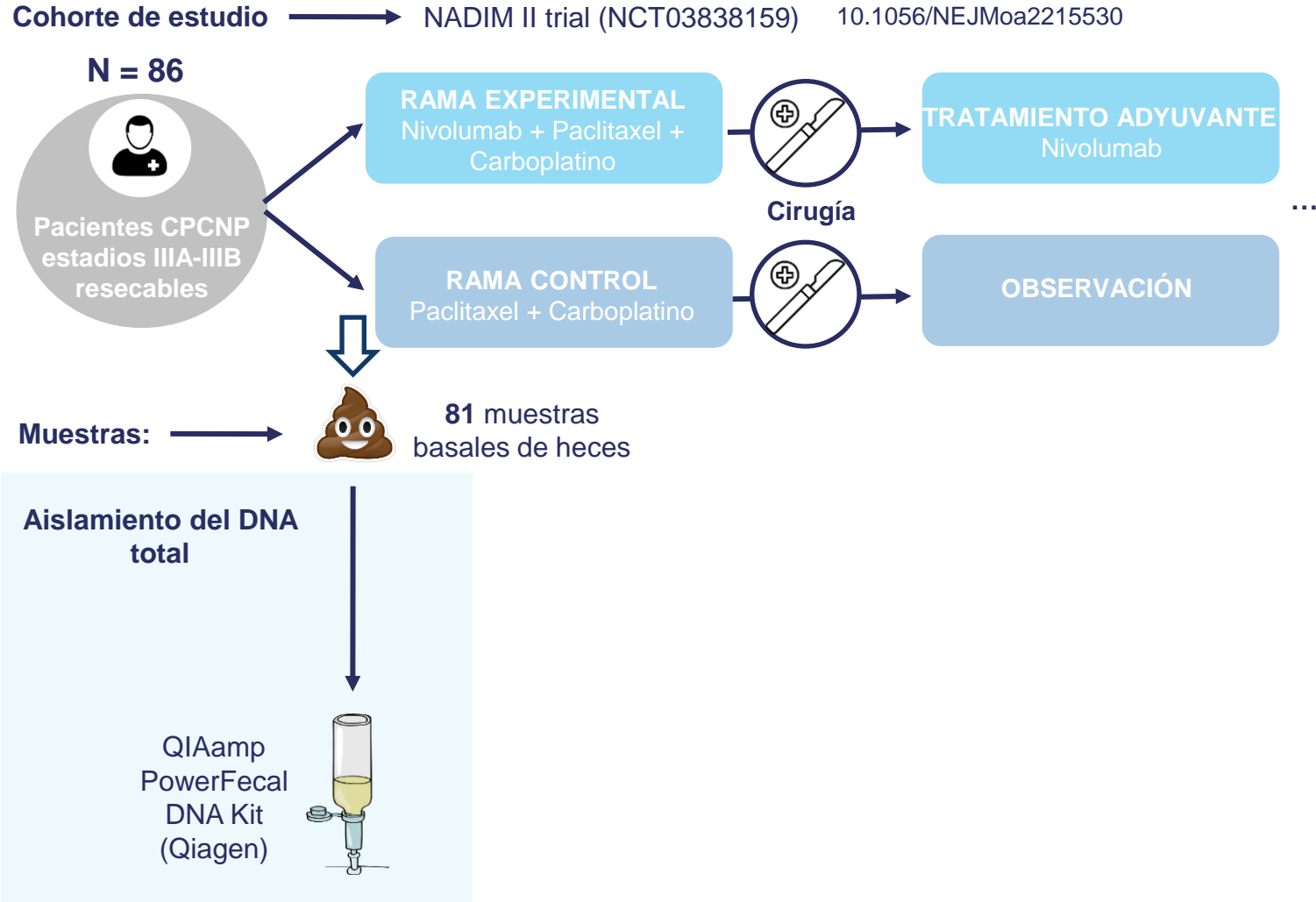
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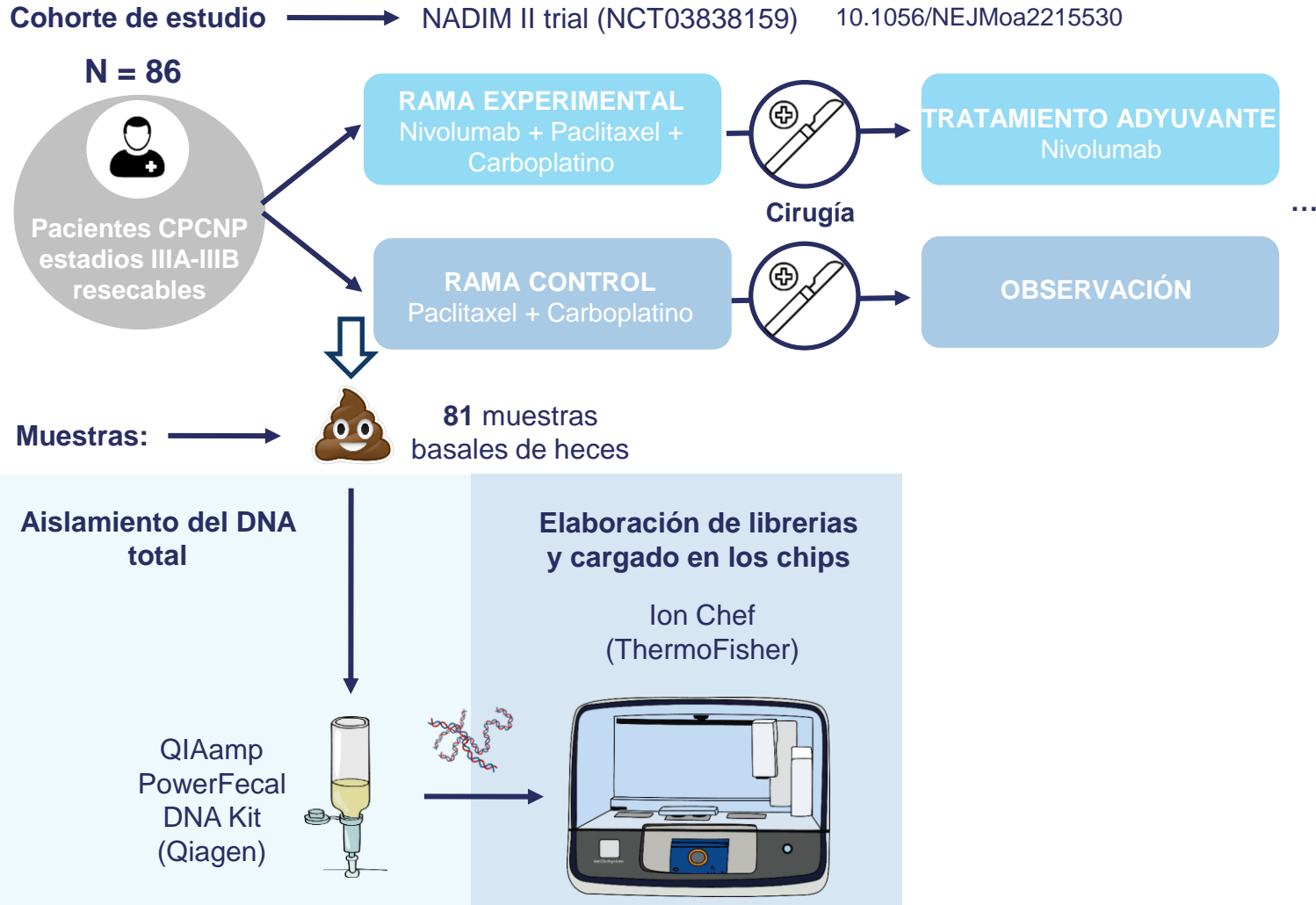
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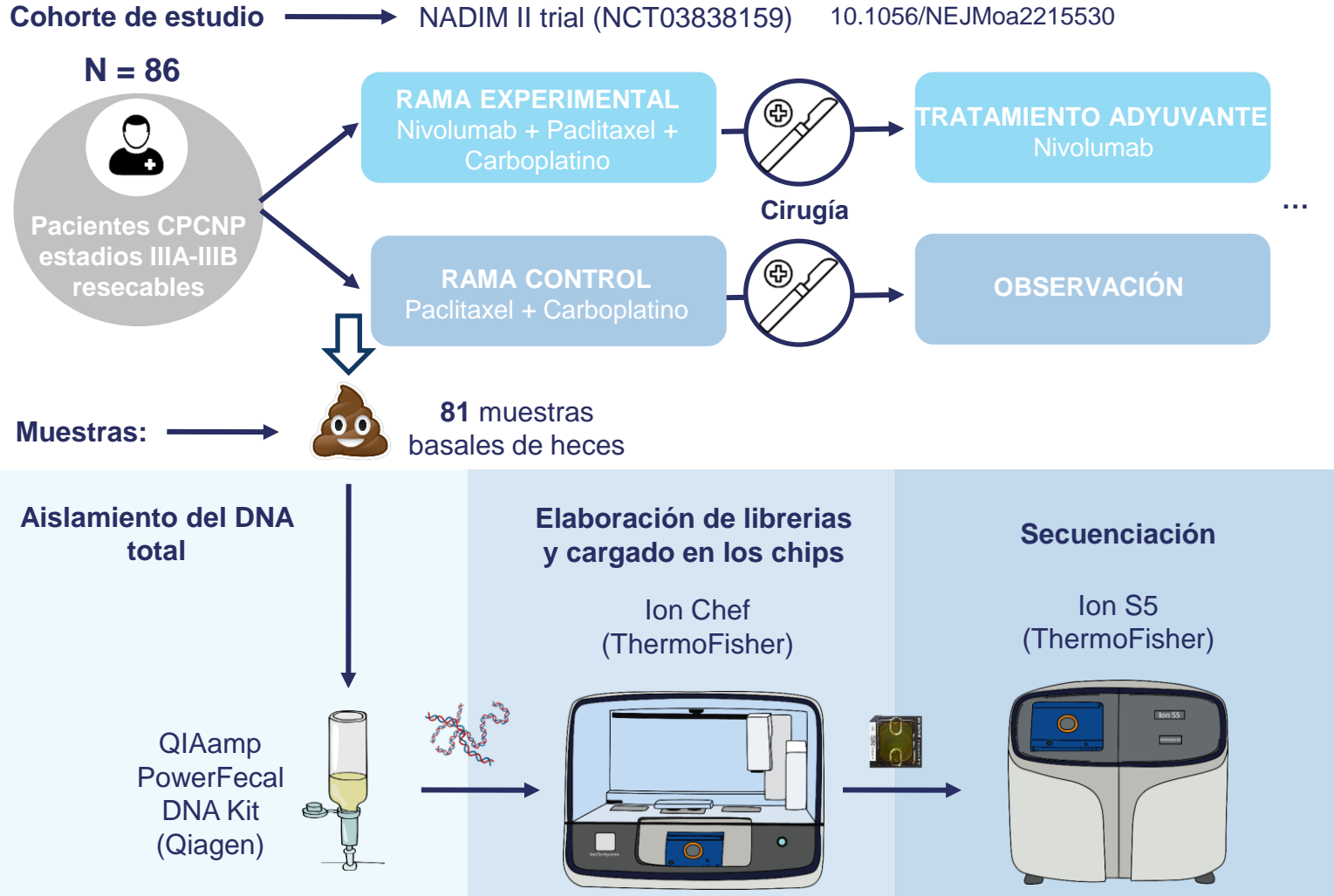
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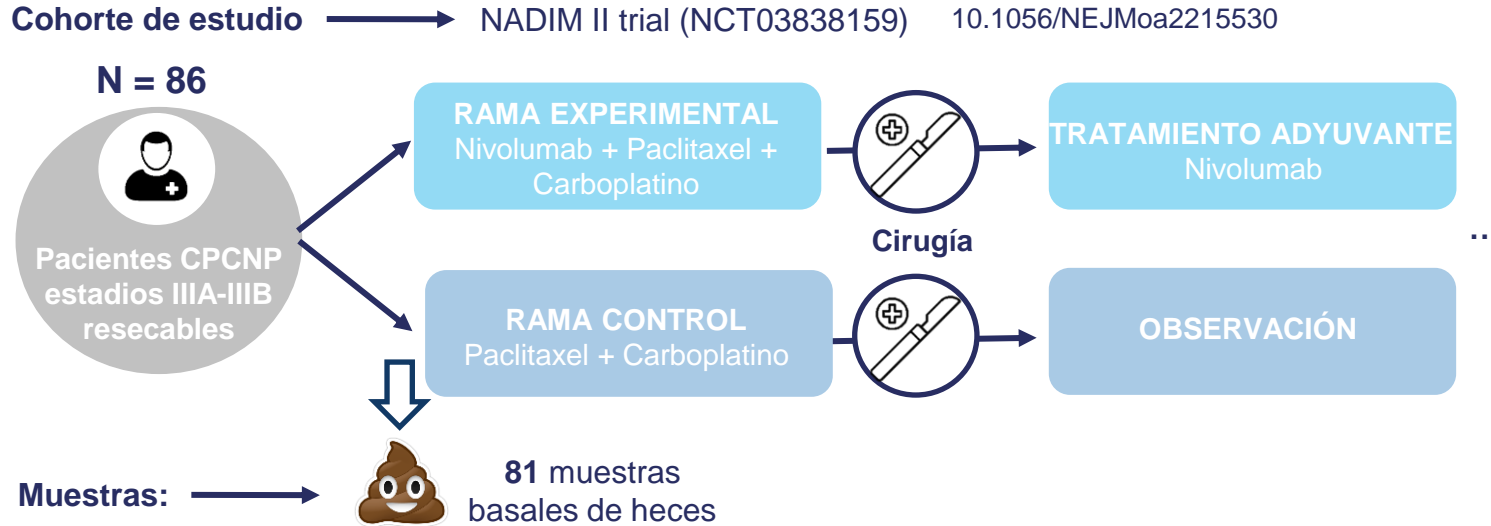
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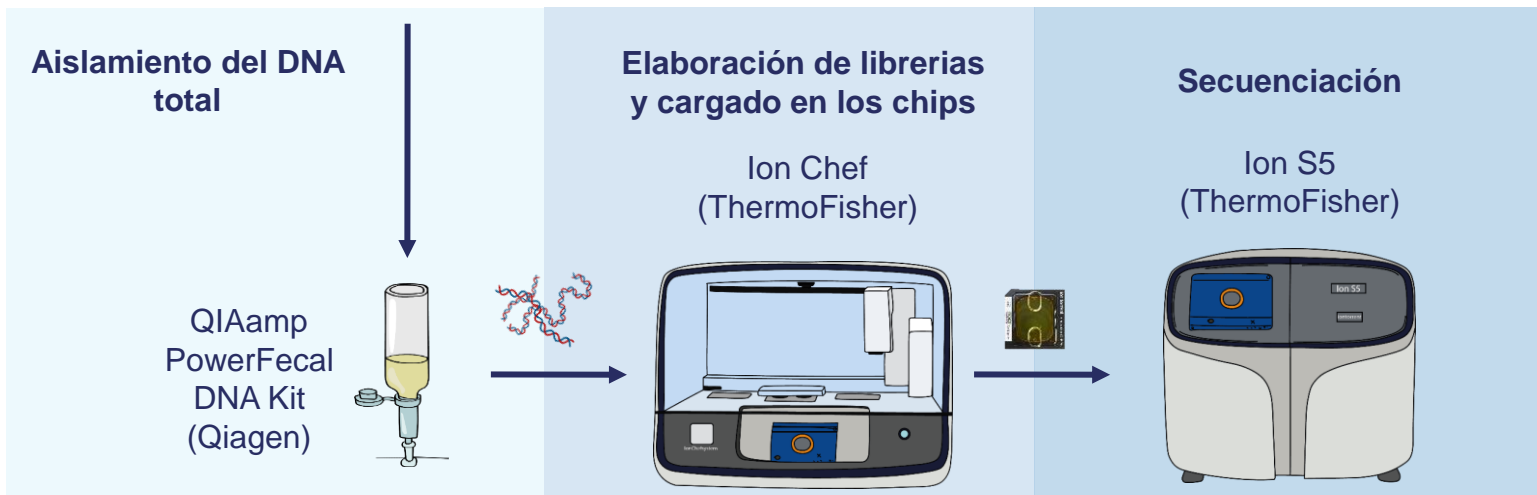
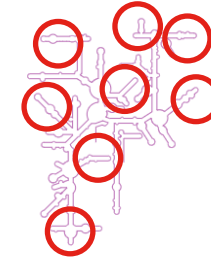
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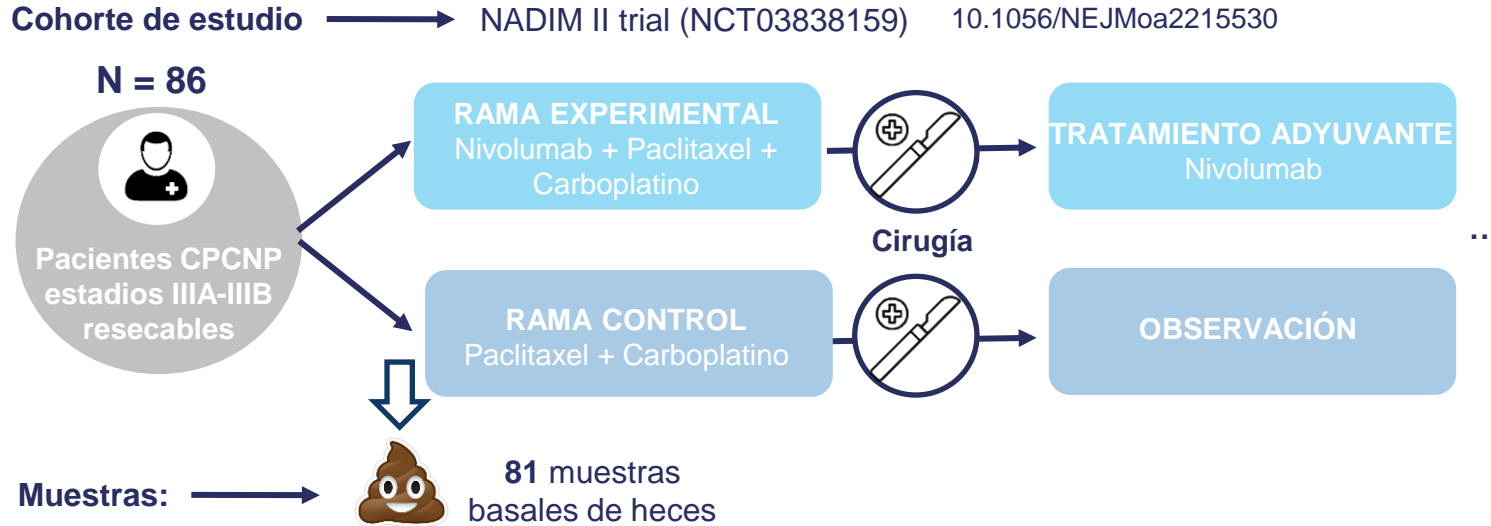
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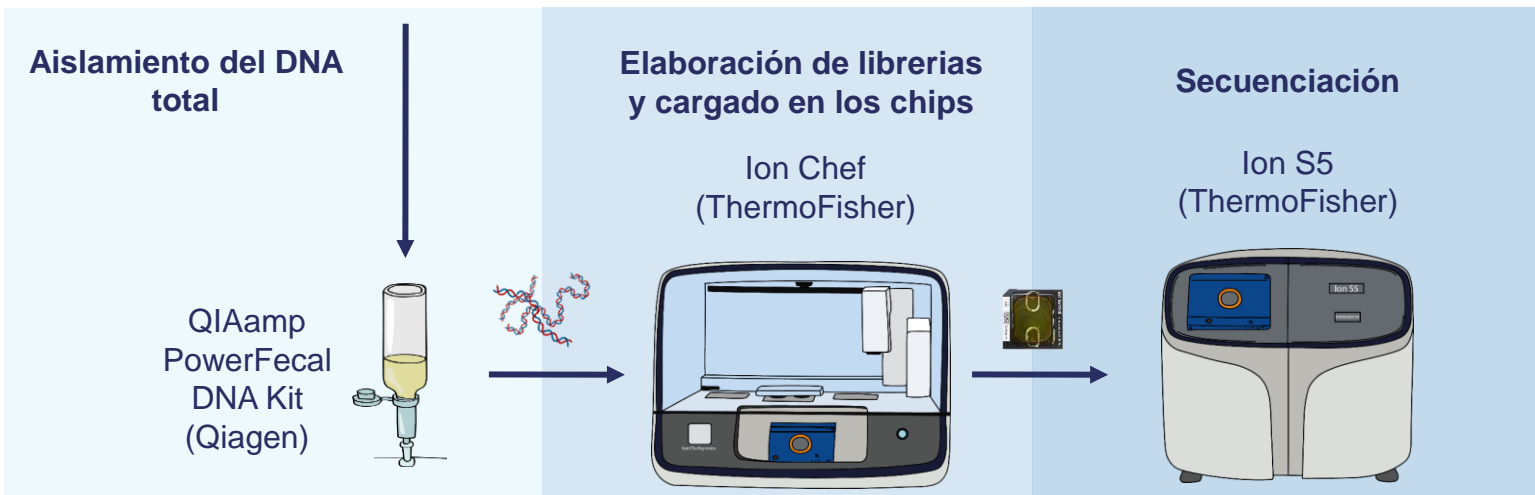
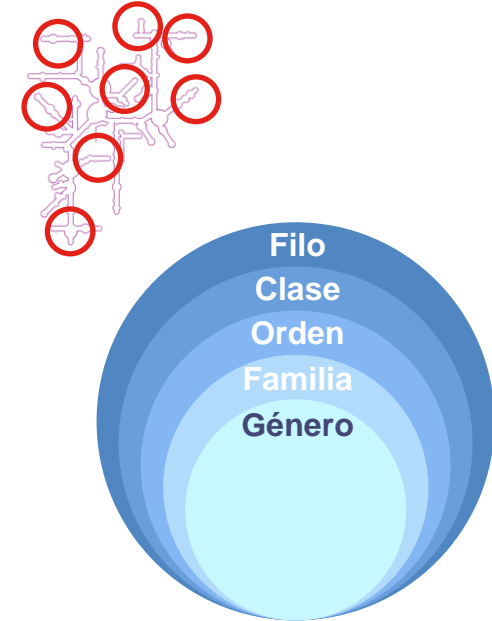
AmpliSeq™ Microbiome Health Research assay



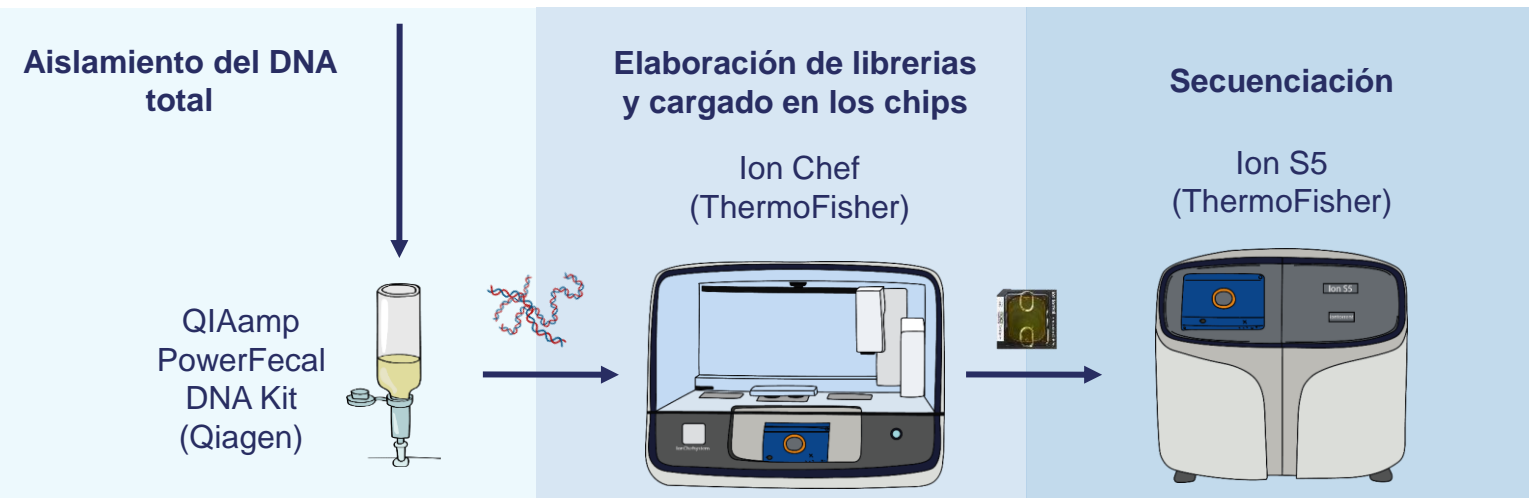
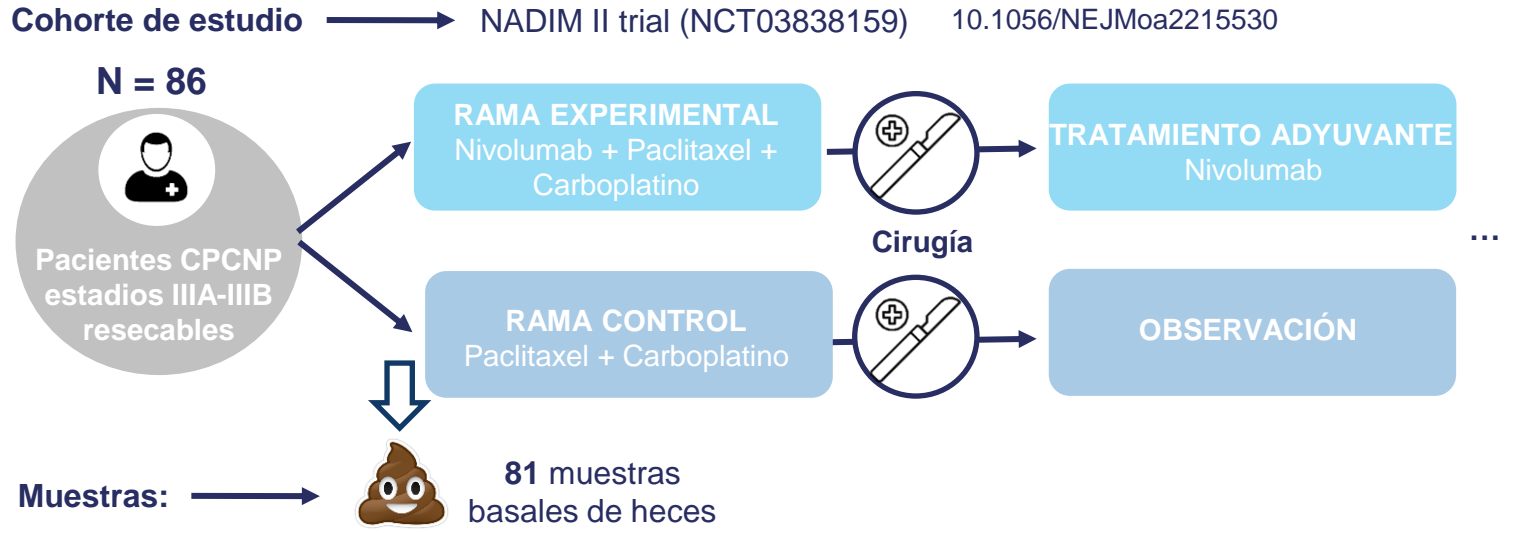
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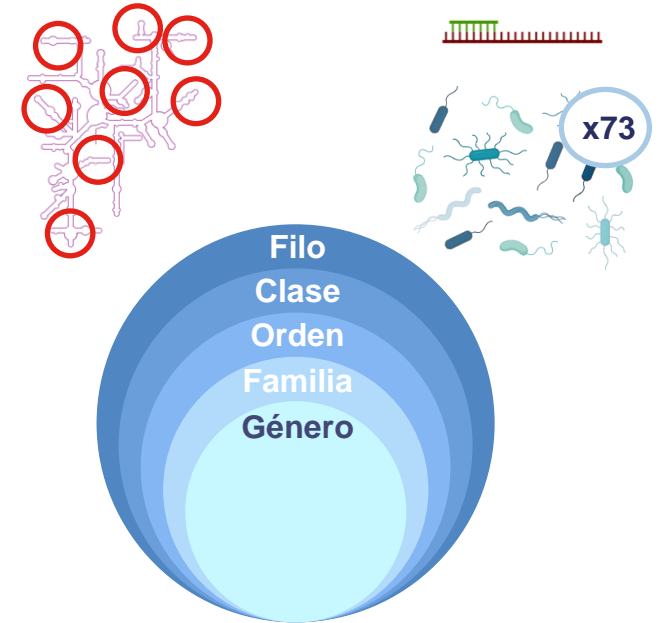
AmpliSeq™ Microbiome Health Research assay



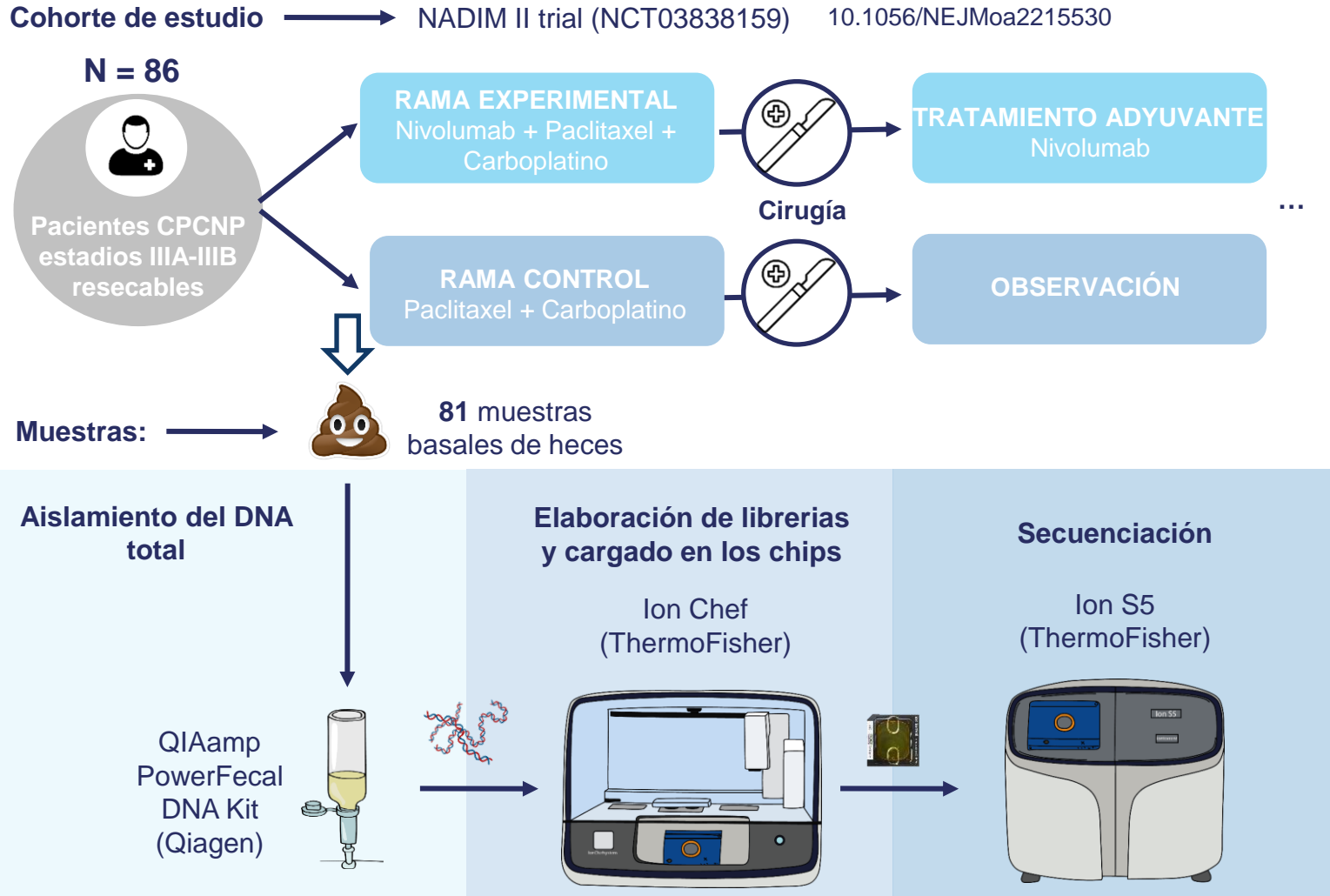
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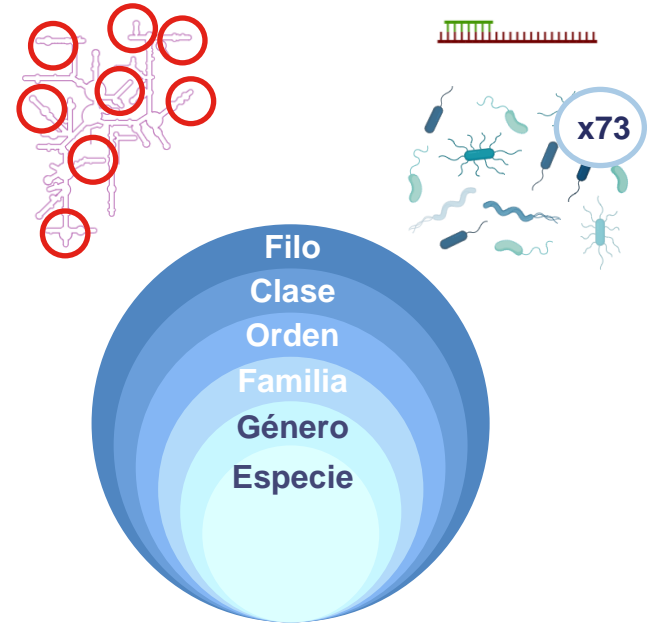
AmpliSeq™ Microbiome Health Research assay



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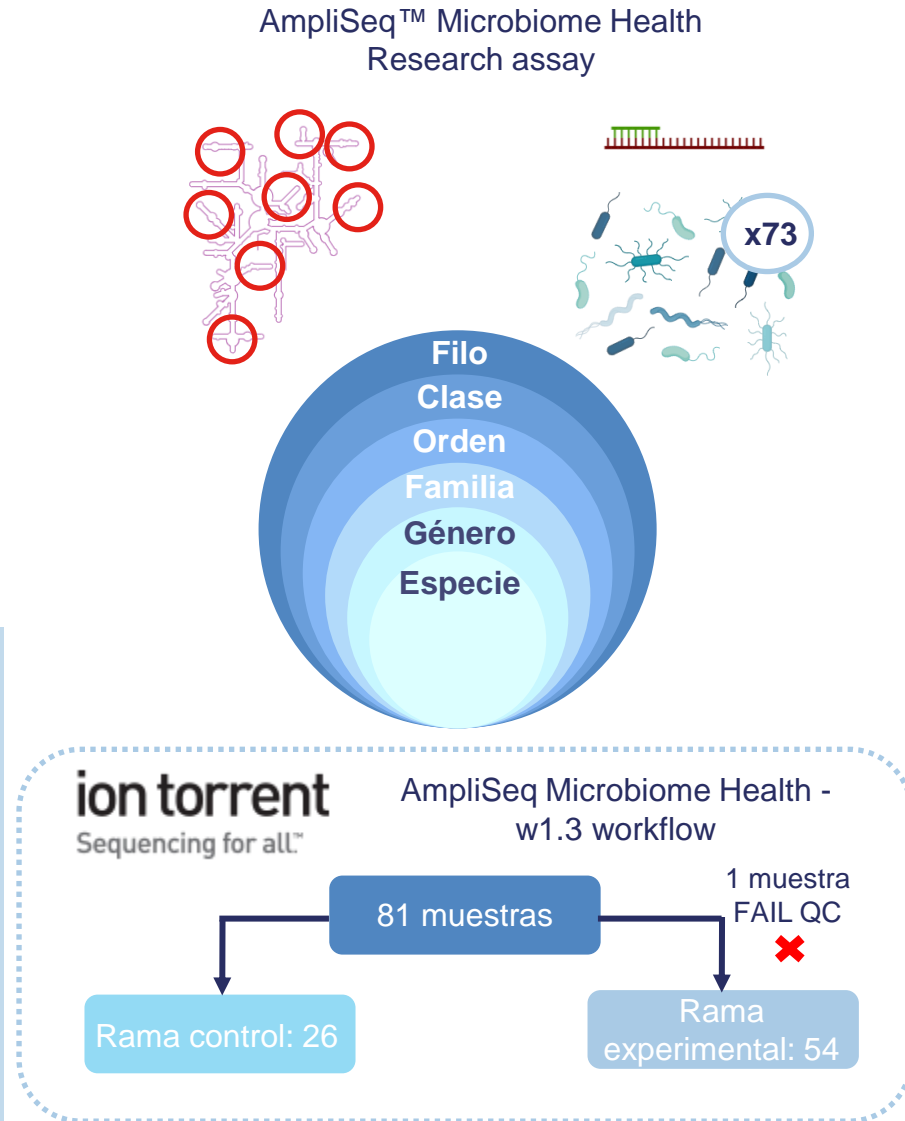
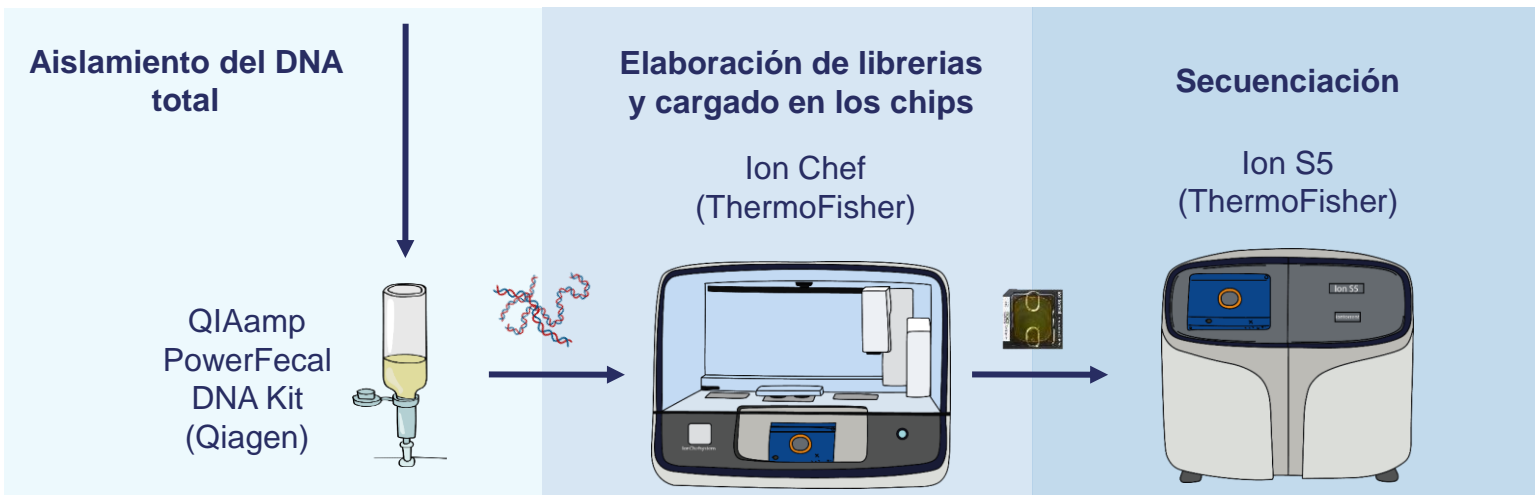
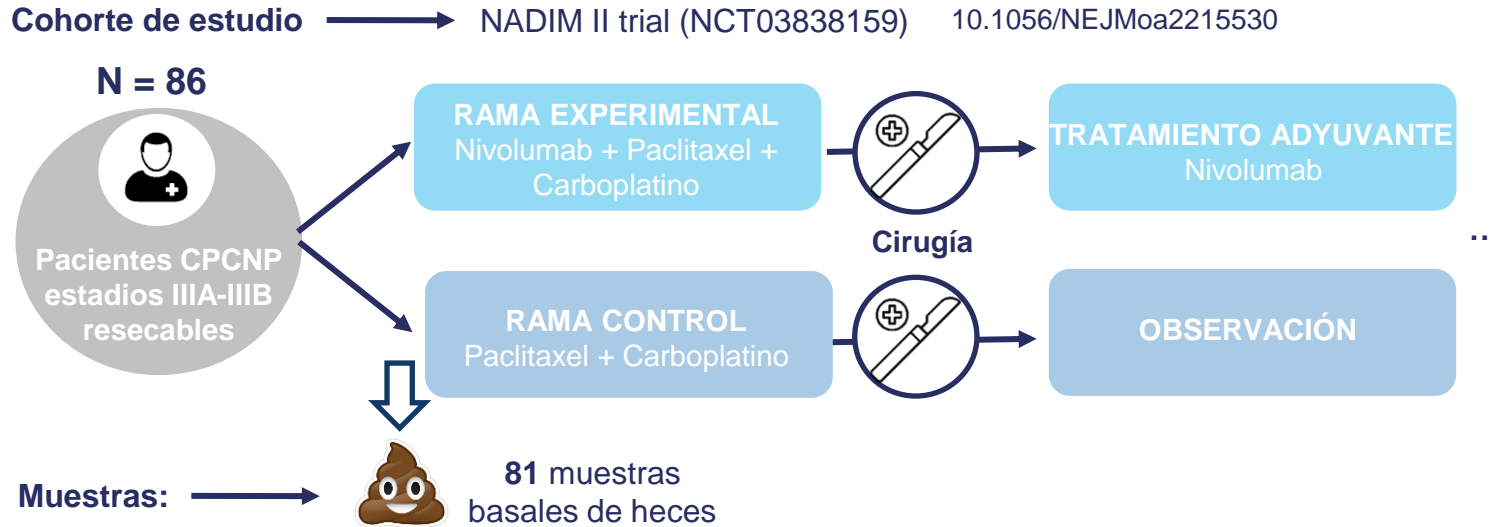


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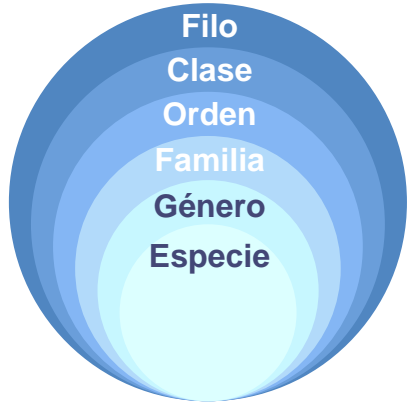


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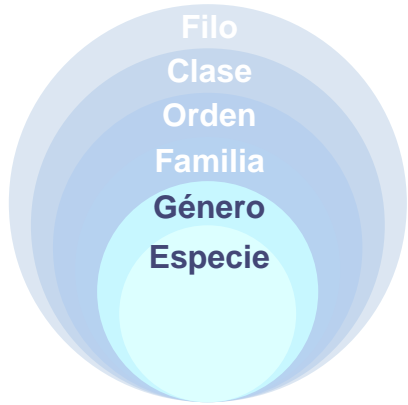


2. Pacientes y metodología





2. Pacientes y metodología



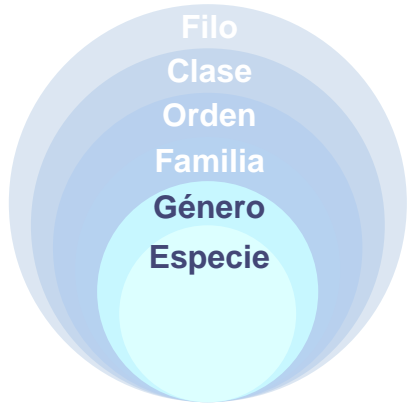
Respuesta
patológica

Supervivencia:
PFS y OS

Efectos
adversos: colitis



2. Pacientes y metodología



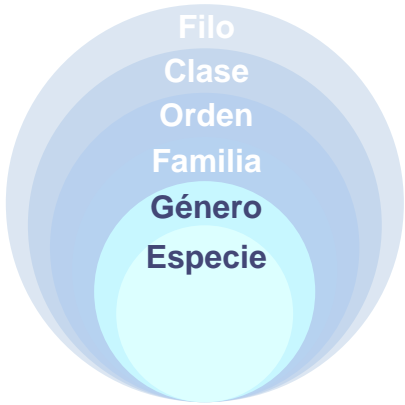
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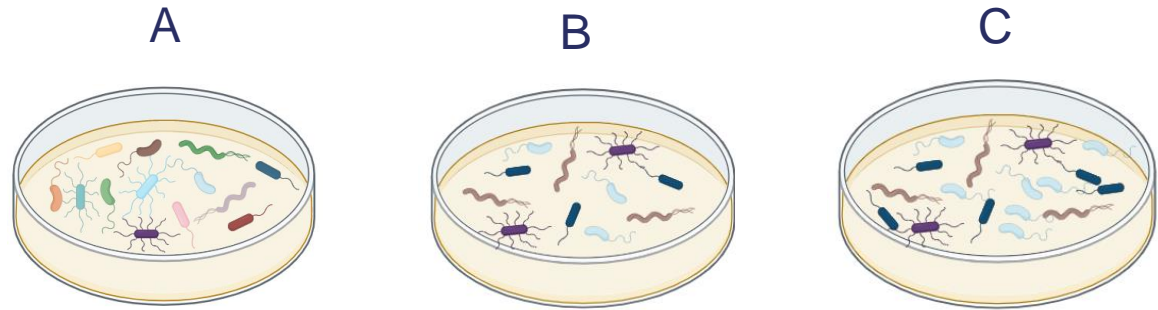
Alfa-diversidad → Diversidad intrínseca de la muestra

2. Pacientes y metodología



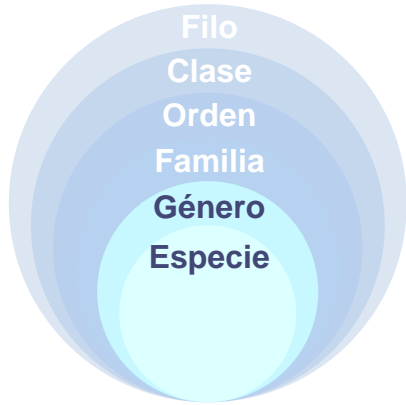
- Respuesta patológica
- Supervivencia: PFS y OS
- Efectos adversos: colitis

Alfa-diversidad → Diversidad intrínseca de la muestra



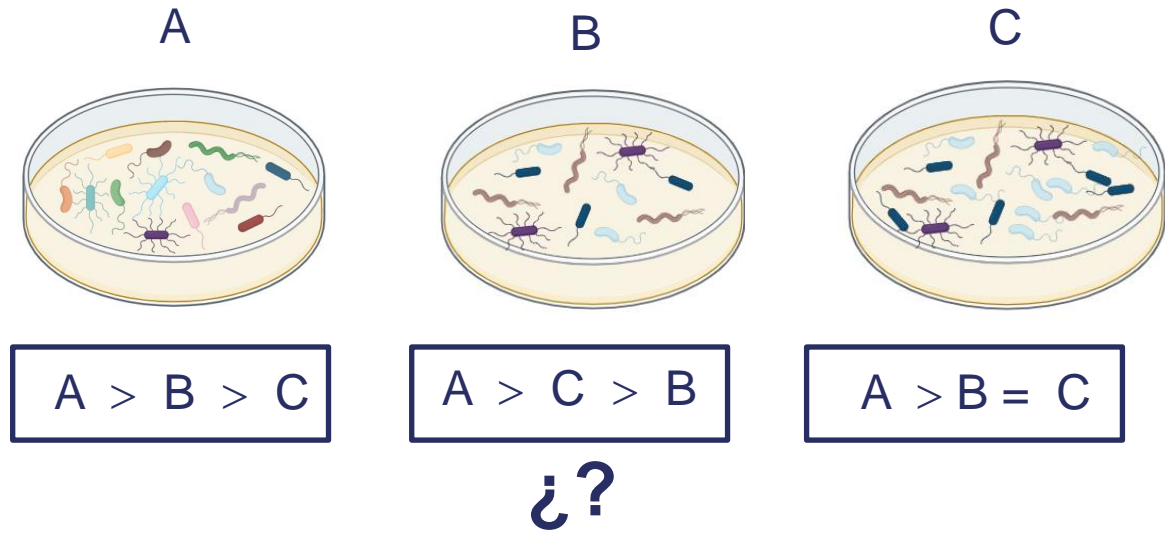


2. Pacientes y metodología



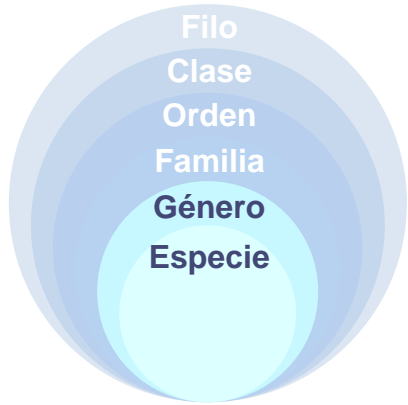
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- Supervivencia: PFS y OS
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Alfa-diversidad → Diversidad intrínseca de la muestra





2. Pacientes y metodología



Respuesta patológica

Supervivencia: PFS y OS

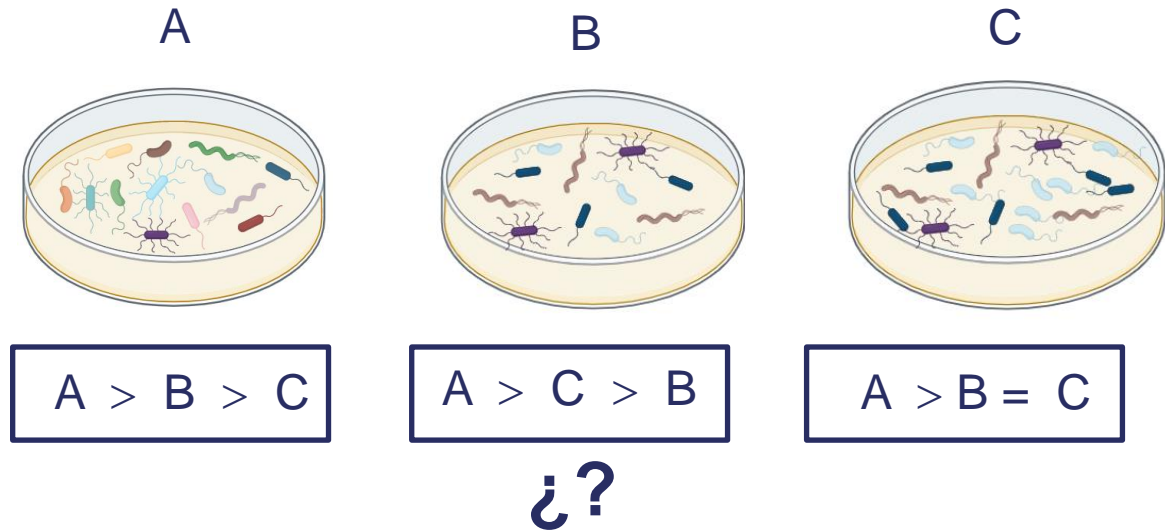
Efectos adversos: colitis

Simpson's diversity

$$D = \frac{\sum n(n-1)}{N(N-1)}$$

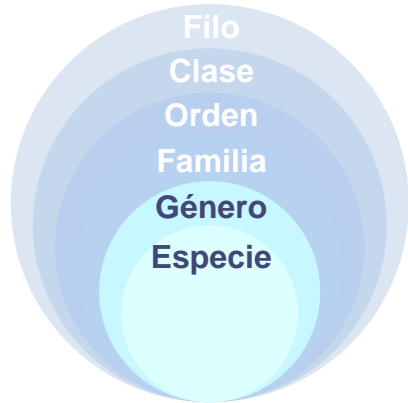
Mide tanto **riqueza** como **abundancia** de especies, dando más peso a las **especies más abundantes**

Alfa-diversidad → Diversidad intrínseca de la muestra





2. Pacientes y metodología



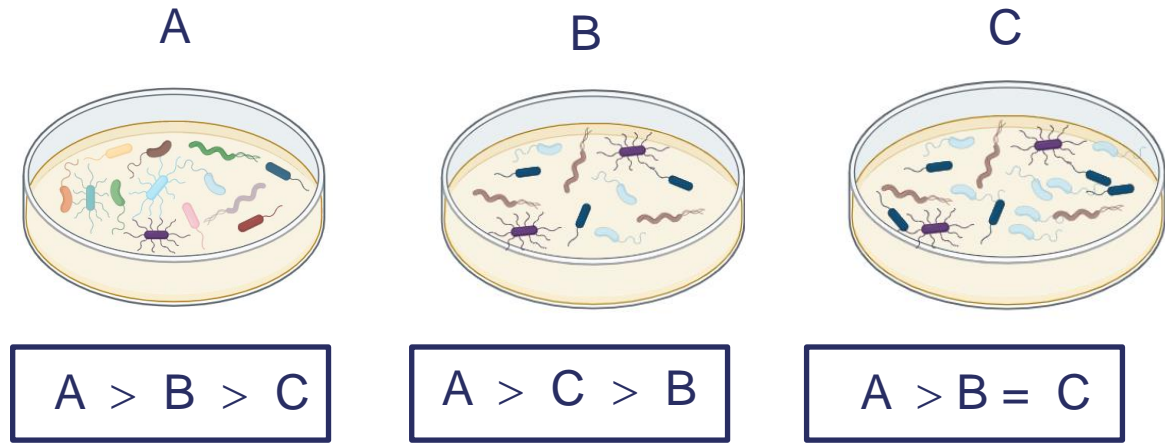
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Alfa-diversidad → Diversidad intrínseca de la muestra



Shannon Index

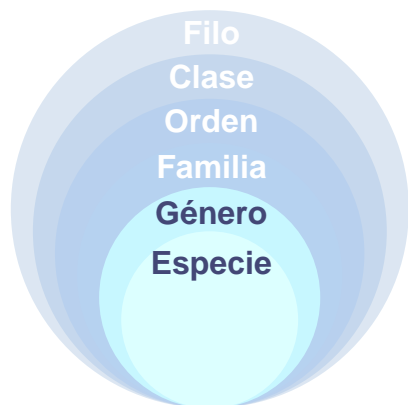
$$H' = - \sum_{i=1}^R p_i \ln p_i$$

¿?

Mide tanto **riqueza** como **abundancia** (menos afectado por la abundancia que el Simpson) de especies



2. Pacientes y metodología



Respuesta patológica

Supervivencia: PFS y OS

Efectos adversos: colitis

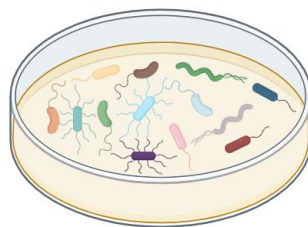
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Alfa-diversidad → Diversidad intrínseca de la muestra

A



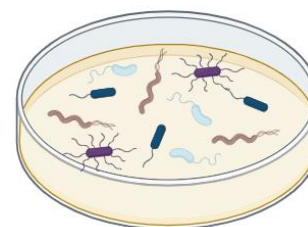
A > B > C

Shannon Index

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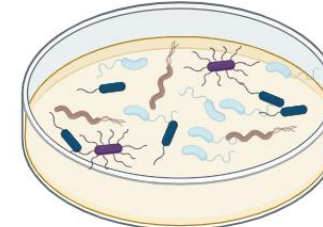
B



A > C > B

¿?

C



A > B = C

Chao1

$$C = \frac{N + S^2}{2D}$$

Mide **riqueza**, da más peso a las **especies menos frecuentes**



3. Resultados

3.1 – Descriptiva



3. Resultados

3.1 – Descriptiva

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Nivolumab plus Chemotherapy (N = 57)	Chemotherapy Alone (N = 29)
Median age (IQR) — yr	65 (58–70)	63 (57–66)
Body-mass index — no. (%)†		
≤25	15 (26)	10 (34)
>25	42 (74)	19 (66)
Female sex — no. (%)	21 (37)	13 (45)
History of tobacco use — no. (%)		
Never smoked	5 (9)	0
Former smoker	22 (39)	8 (28)
Current smoker	30 (53)	21 (72)
ECOG performance-status score — no. (%)‡		
0	31 (54)	16 (55)
1	26 (46)	13 (45)
Histologic type — no. (%)		
Adenocarcinoma	25 (44)	11 (38)
Adenosquamous carcinoma	1 (2)	0
Squamous-cell carcinoma	21 (37)	14 (48)
Large-cell carcinoma	2 (4)	1 (3)
Not otherwise specified or undifferentiated	7 (12)	2 (7)
Other	1 (2)	1 (3)
TNM classification — no. (%)§		
T1N2M0	12 (21)	4 (14)
T2N2M0	16 (28)	7 (24)
T3N1M0	2 (4)	1 (3)
T3N2M0	13 (23)	5 (17)
T4N0M0	6 (11)	9 (31)
T4N1M0	8 (14)	3 (10)
Median tumor size (range) — mm	50 (15–155)	52 (15–166)
Node stage — no. (%)		
N0	6 (11)	9 (31)
N1	10 (18)	4 (14)
N2	41 (72)	16 (55)
N2, multiple stations	22 (39)	11 (38)



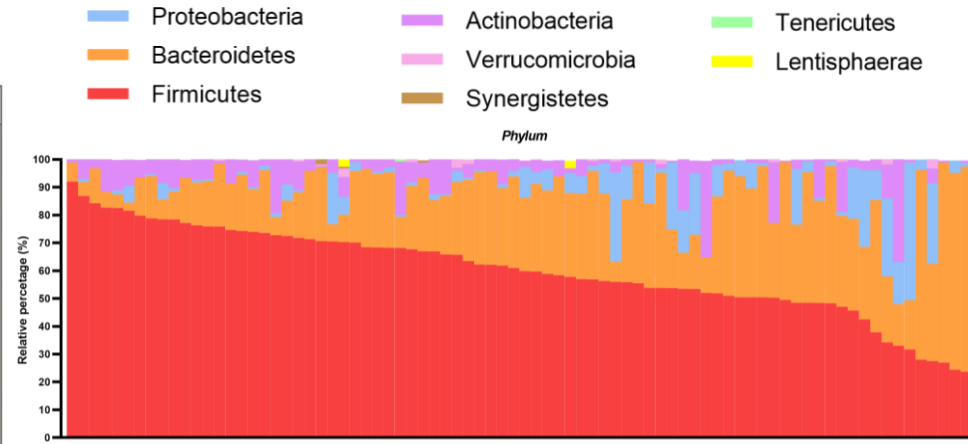
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Nivel taxonómico: Filo





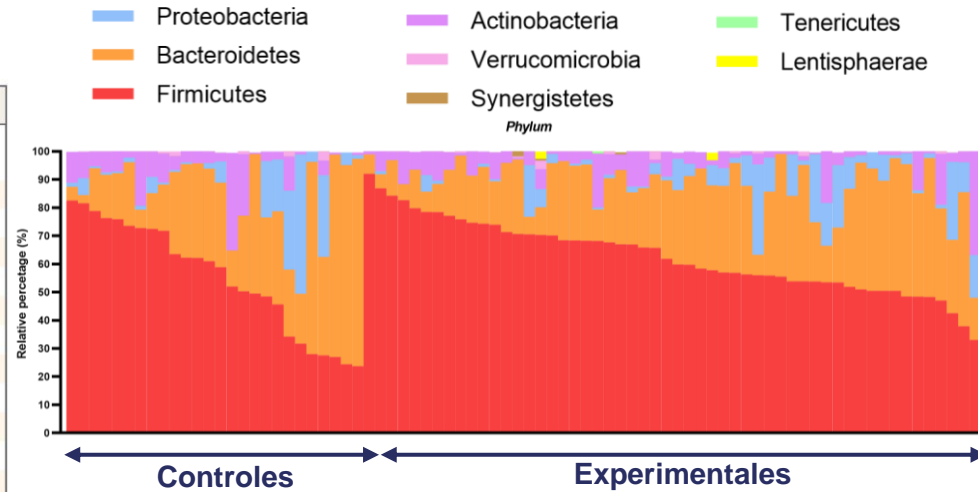
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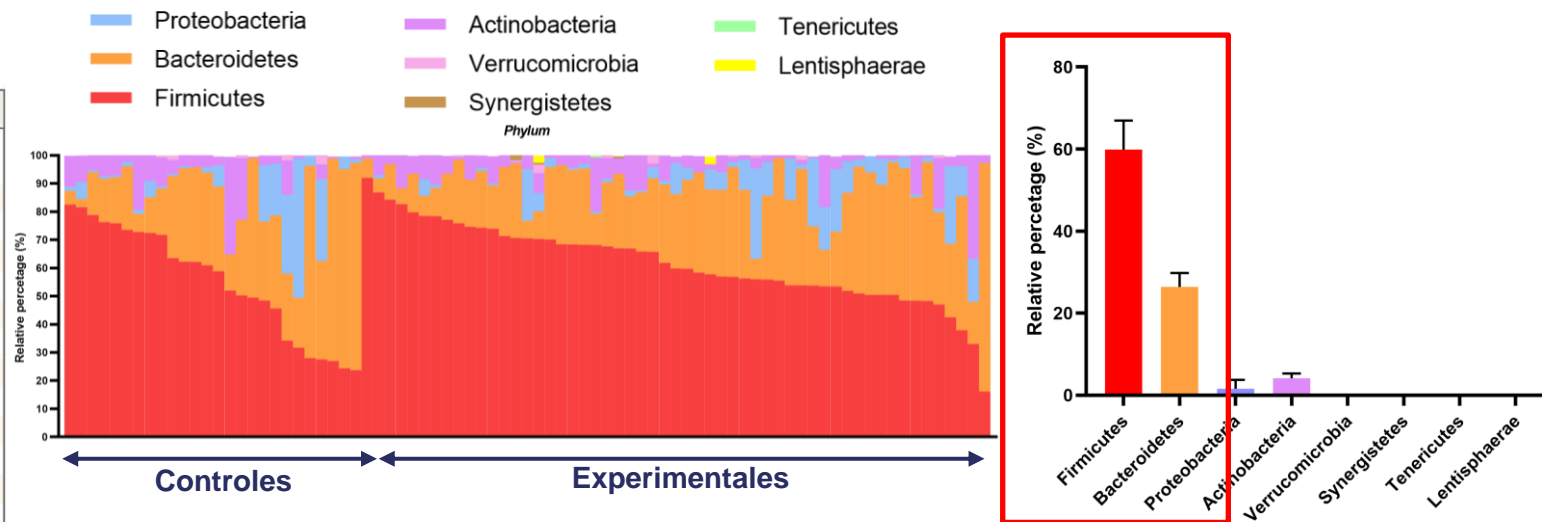
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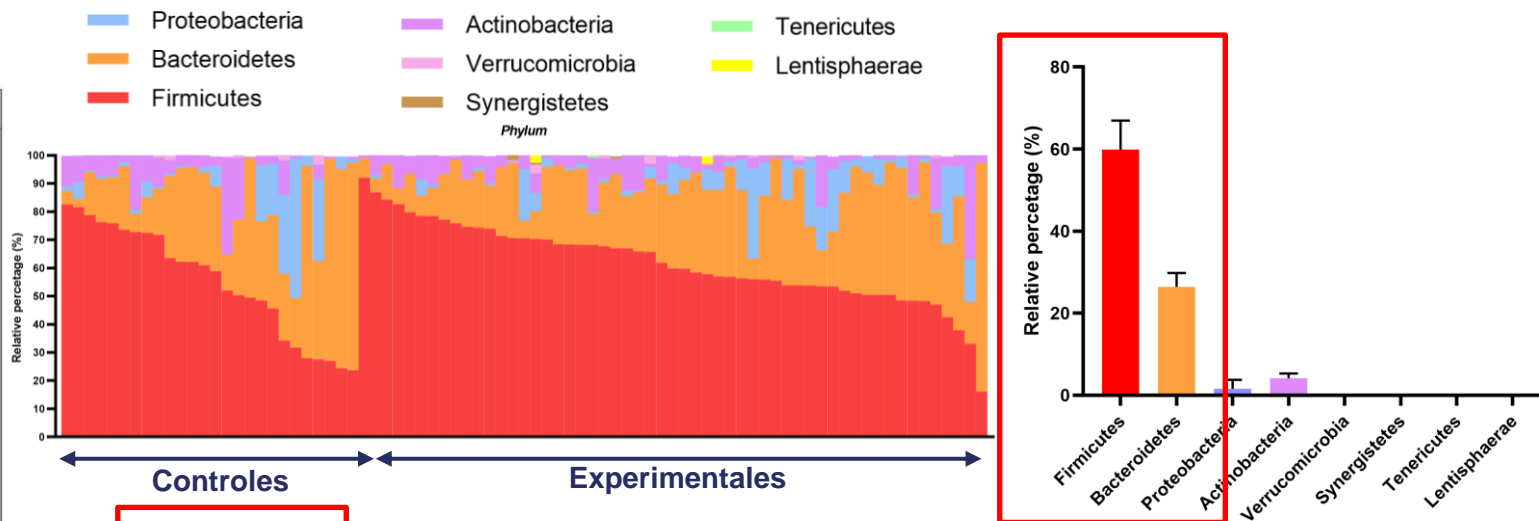
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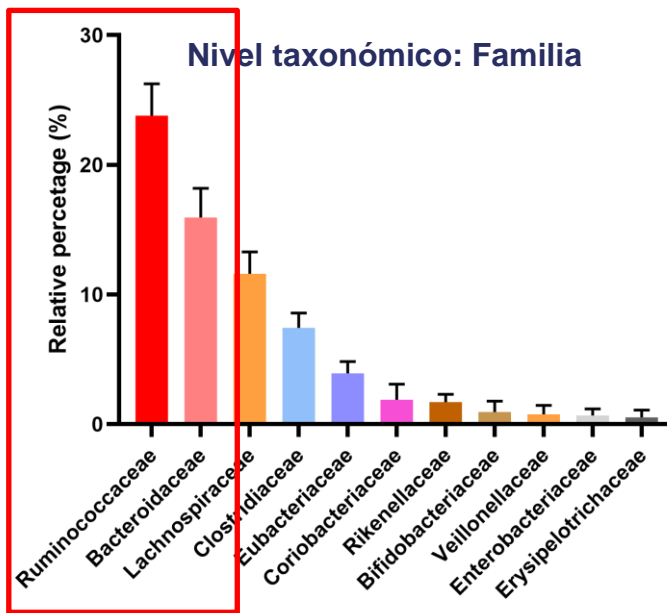
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Body-mass index — no. (%)†		
≤25	15 (26)	10 (34)
>25	42 (74)	19 (66)
Female sex — no. (%)	21 (37)	13 (45)
History of tobacco use — no. (%)		
Never smoked	5 (9)	0
Former smoker	22 (39)	8 (28)
Current smoker	30 (53)	21 (72)
ECOG performance-status score — no. (%)‡		
0	31 (54)	16 (55)
1	26 (46)	13 (45)
Histologic type — no. (%)		
Adenocarcinoma	25 (44)	11 (38)
Adenosquamous carcinoma	1 (2)	0
Squamous-cell carcinoma	21 (37)	14 (48)
Large-cell carcinoma	2 (4)	1 (3)
Not otherwise specified or undifferentiated	7 (12)	2 (7)
Other	1 (2)	1 (3)
TNM classification — no. (%)§		
T1N2M0	12 (21)	4 (14)
T2N2M0	16 (28)	7 (24)
T3N1M0	2 (4)	1 (3)
T3N2M0	13 (23)	5 (17)
T4N0M0	6 (11)	9 (31)
T4N1M0	8 (14)	3 (10)
Median tumor size (range) — mm	50 (15–155)	52 (15–166)
Node stage — no. (%)		
N0	6 (11)	9 (31)
N1	10 (18)	4 (14)
N2	41 (72)	16 (55)
N2, multiple stations	22 (39)	11 (38)

Nivel taxonómico: Filo



Nivel taxonómico: Familia



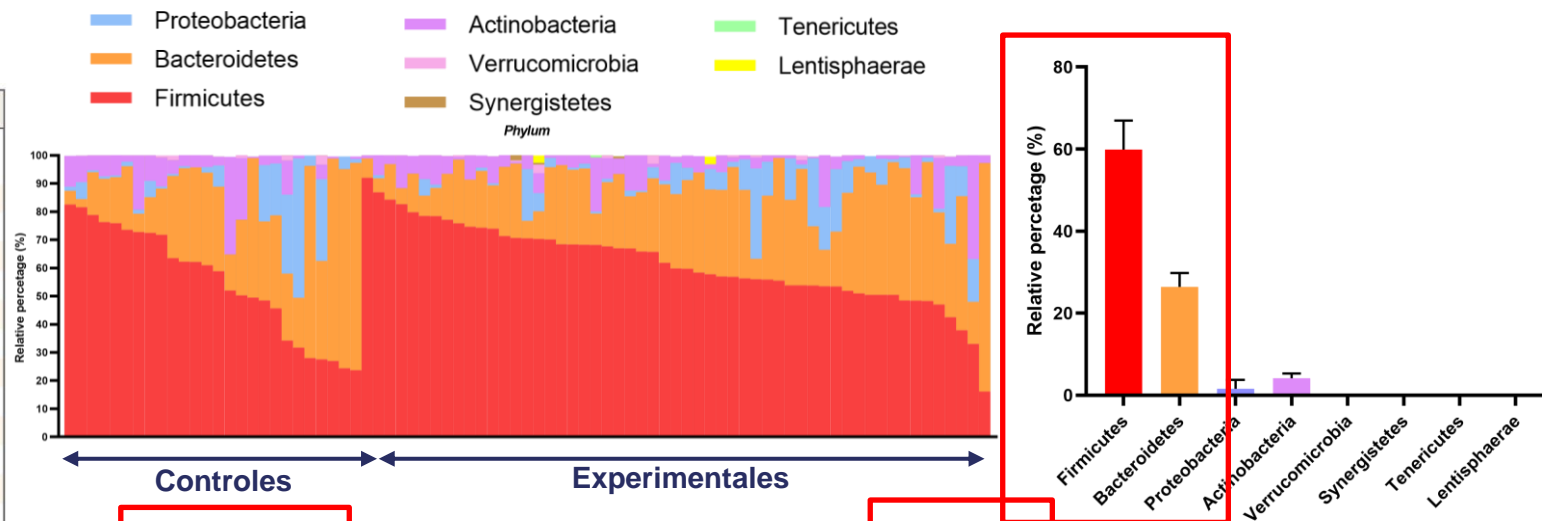
3. Resultados

3.1 – Descriptiva

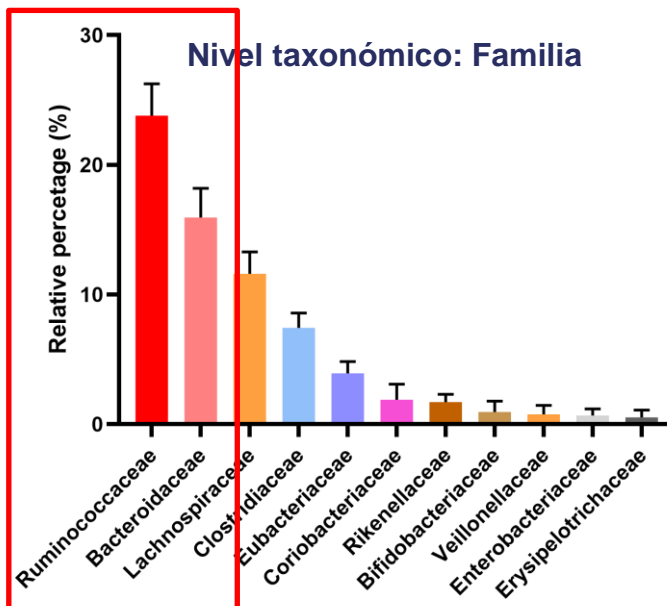
Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	Nivolumab plus Chemotherapy (N=57)	Chemotherapy Alone (N=29)
Median age (IQR) — yr	65 (58–70)	63 (57–66)
Body-mass index — no. (%)†		
≤25	15 (26)	10 (34)
>25	42 (74)	19 (66)
Female sex — no. (%)	21 (37)	13 (45)
History of tobacco use — no. (%)		
Never smoked	5 (9)	0
Former smoker	22 (39)	8 (28)
Current smoker	30 (53)	21 (72)
ECOG performance-status score — no. (%)‡		
0	31 (54)	16 (55)
1	26 (46)	13 (45)
Histologic type — no. (%)		
Adenocarcinoma	25 (44)	11 (38)
Adenosquamous carcinoma	1 (2)	0
Squamous-cell carcinoma	21 (37)	14 (48)
Large-cell carcinoma	2 (4)	1 (3)
Not otherwise specified or undifferentiated	7 (12)	2 (7)
Other	1 (2)	1 (3)
TNM classification — no. (%)§		
T1N2M0	12 (21)	4 (14)
T2N2M0	16 (28)	7 (24)
T3N1M0	2 (4)	1 (3)
T3N2M0	13 (23)	5 (17)
T4N0M0	6 (11)	9 (31)
T4N1M0	8 (14)	3 (10)
Median tumor size (range) — mm	50 (15–155)	52 (15–166)
Node stage — no. (%)		
N0	6 (11)	9 (31)
N1	10 (18)	4 (14)
N2	41 (72)	16 (55)
N2, multiple stations	22 (39)	11 (38)

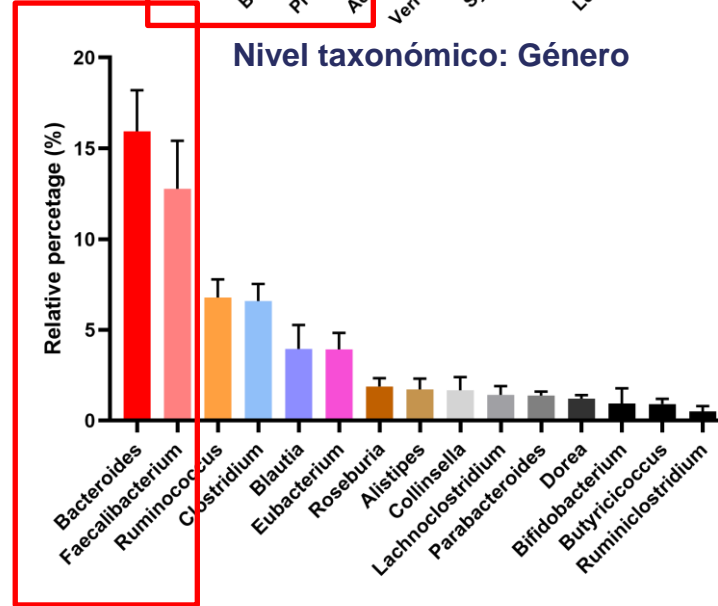
Nivel taxonómico: Filo



Nivel taxonómico: Familia



Nivel taxonómico: Género





3. Resultados

3.2 – Alfa-diversidad como pronóstico



3. Resultados

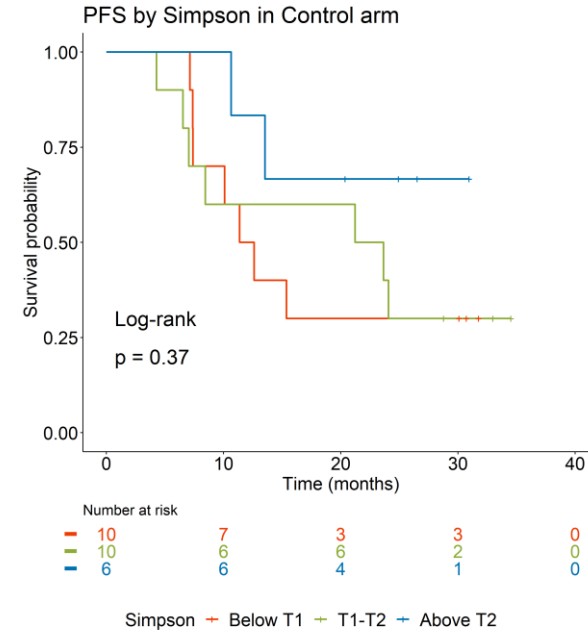
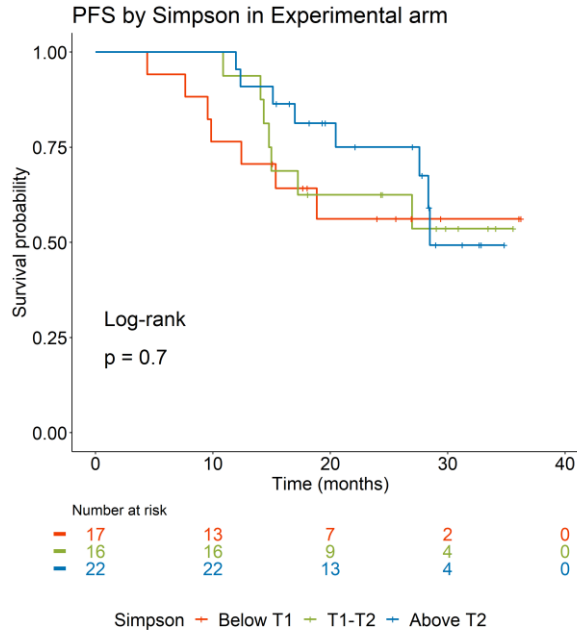
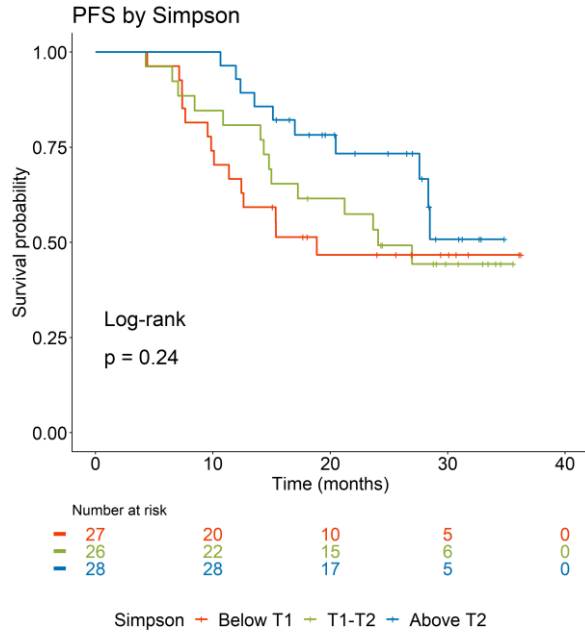
3.2 – Alfa-diversidad como pronóstico

	Progression-Free Survival						Overall Survival					
	All patients		Experimental		Control		All patients		Experimental		Control	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
<i>Simpson</i>	0,51 (0,23-1,15)	0,106	0,65 (0,23-1,79)	0,401	0,35 (0,07-1,67)	0,186	0,89 (0,33-2,38)	0,818	1,40 (0,35-5,61)	0,635	0,71 (0,14-3,69)	0,683
<i>Shannon</i>	0,61 (0,27-1,39)	0,241	0,84 (0,30-2,31)	0,735	0,33 (0,07-1,62)	0,174	1,20 (0,46-3,12)	0,708	2,17 (0,56-8,42)	0,261	0,65 (0,12-3,36)	0,606
<i>Chao1</i>	0,44 (0,19-1,00)	0,05	0,54 (0,19-1,52)	0,244	0,30 (0,08-1,16)	0,08	0,61 (0,20-1,86)	0,381	1,05 (0,26-4,23)	0,94	0,24 (0,03-2,17)	0,205



3. Resultados

3.2 – Alfa-diversidad como pronóstico

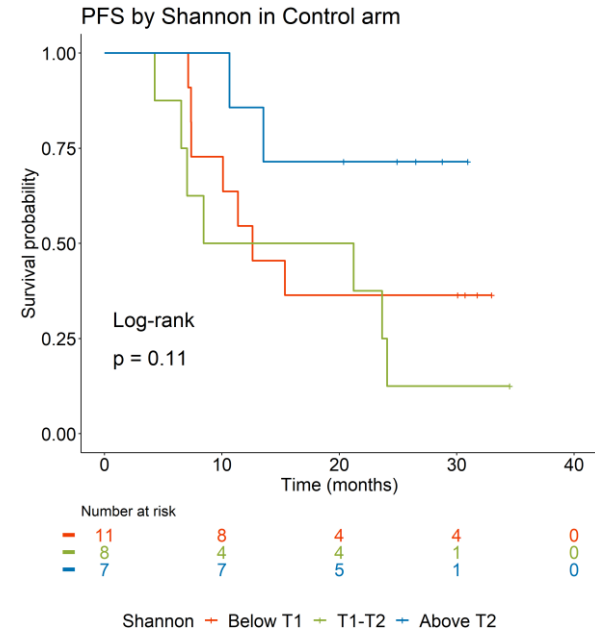
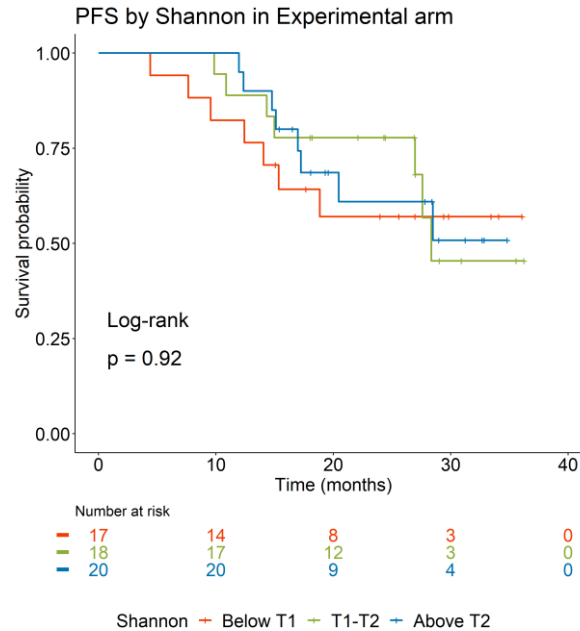
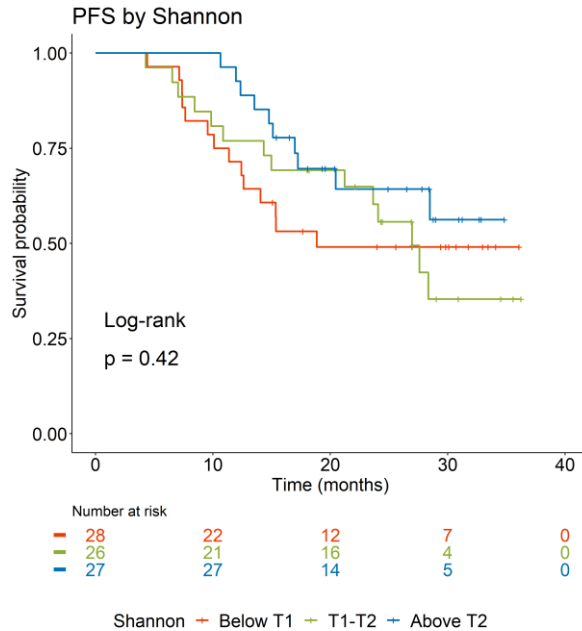


	Progression-Free Survival						Overall Survival					
	All patients		Experimental		Control		All patients		Experimental		Control	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Simpson	0,51 (0,23-1,15)	0,106	0,65 (0,23-1,79)	0,401	0,35 (0,07-1,67)	0,186	0,89 (0,33-2,38)	0,818	1,40 (0,35-5,61)	0,635	0,71 (0,14-3,69)	0,683
Shannon	0,61 (0,27-1,39)	0,241	0,84 (0,30-2,31)	0,735	0,33 (0,07-1,62)	0,174	1,20 (0,46-3,12)	0,708	2,17 (0,56-8,42)	0,261	0,65 (0,12-3,36)	0,606
Chao1	0,44 (0,19-1,00)	0,05	0,54 (0,19-1,52)	0,244	0,30 (0,08-1,16)	0,08	0,61 (0,20-1,86)	0,381	1,05 (0,26-4,23)	0,94	0,24 (0,03-2,17)	0,205



3. Resultados

3.2 – Alfa-diversidad como pronóstico

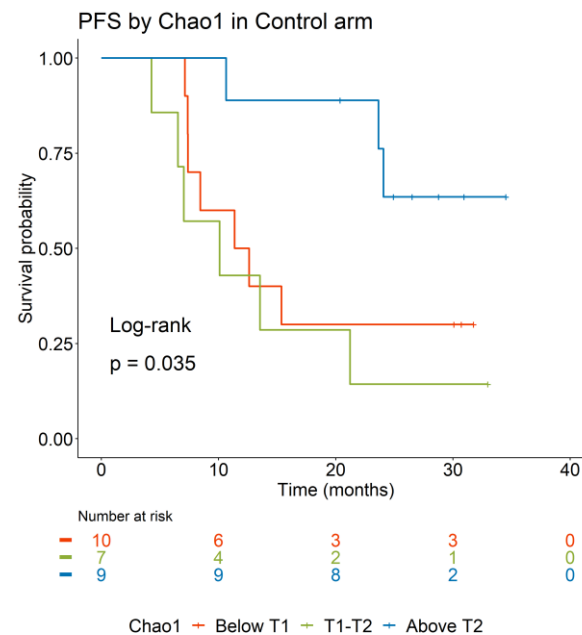
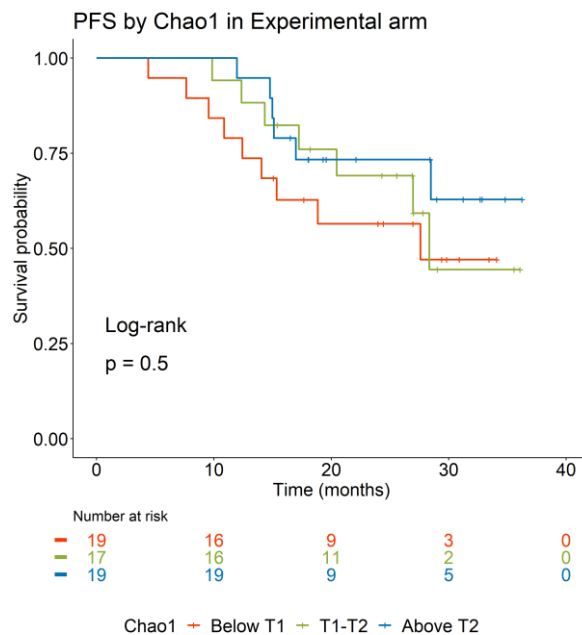
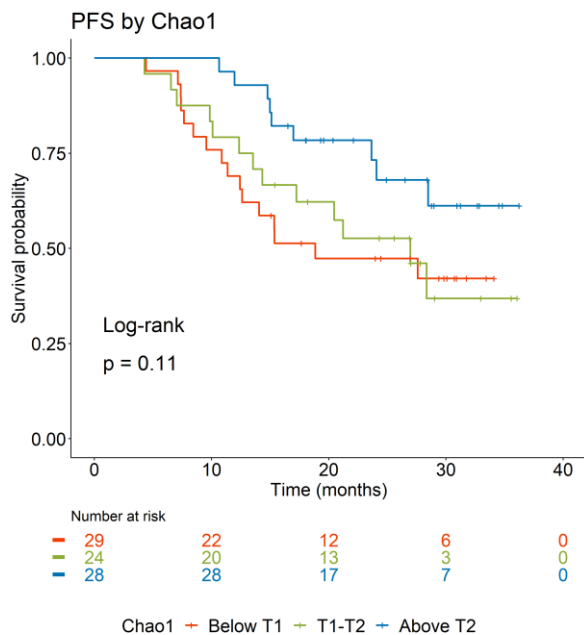


	Progression-Free Survival						Overall Survival					
	All patients		Experimental		Control		All patients		Experimental		Control	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Simpson	0,51 (0,23-1,15)	0,106	0,65 (0,23-1,79)	0,401	0,35 (0,07-1,67)	0,186	0,89 (0,33-2,38)	0,818	1,40 (0,35-5,61)	0,635	0,71 (0,14-3,69)	0,683
Shannon	0,61 (0,27-1,39)	0,241	0,84 (0,30-2,31)	0,735	0,33 (0,07-1,62)	0,174	1,20 (0,46-3,12)	0,708	2,17 (0,56-8,42)	0,261	0,65 (0,12-3,36)	0,606
Chao1	0,44 (0,19-1,00)	0,05	0,54 (0,19-1,52)	0,244	0,30 (0,08-1,16)	0,08	0,61 (0,20-1,86)	0,381	1,05 (0,26-4,23)	0,94	0,24 (0,03-2,17)	0,205



3. Resultados

3.2 – Alfa-diversidad como pronóstico



	Progression-Free Survival						Overall Survival					
	All patients		Experimental		Control		All patients		Experimental		Control	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Simpson	0,51 (0,23-1,15)	0,106	0,65 (0,23-1,79)	0,401	0,35 (0,07-1,67)	0,186	0,89 (0,33-2,38)	0,818	1,40 (0,35-5,61)	0,635	0,71 (0,14-3,69)	0,683
Shannon	0,61 (0,27-1,39)	0,241	0,84 (0,30-2,31)	0,735	0,33 (0,07-1,62)	0,174	1,20 (0,46-3,12)	0,708	2,17 (0,56-8,42)	0,261	0,65 (0,12-3,36)	0,606
Chao1	0,44 (0,19-1,00)	0,05	0,54 (0,19-1,52)	0,244	0,30 (0,08-1,16)	0,08	0,61 (0,20-1,86)	0,381	1,05 (0,26-4,23)	0,94	0,24 (0,03-2,17)	0,205

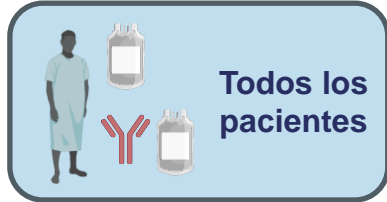


3. Resultados

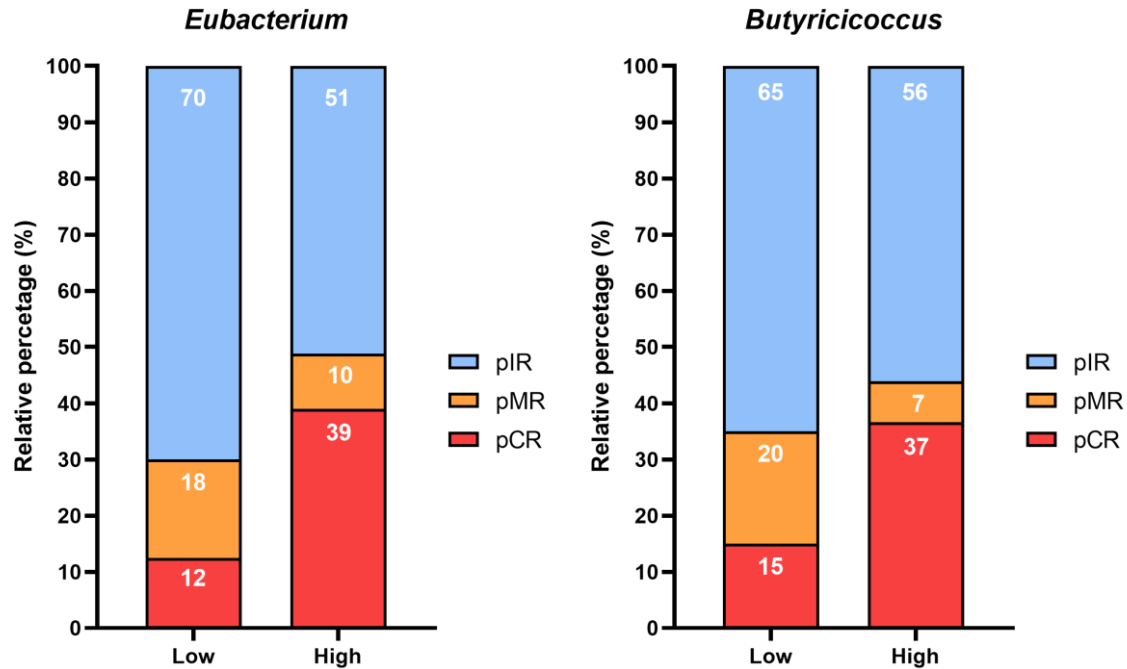
3.3 – Asociación a respuesta patológica y supervivencia

3. Resultados

3.3 – Asociación a respuesta patológica y supervivencia



Respuesta patológica completa (pCR)



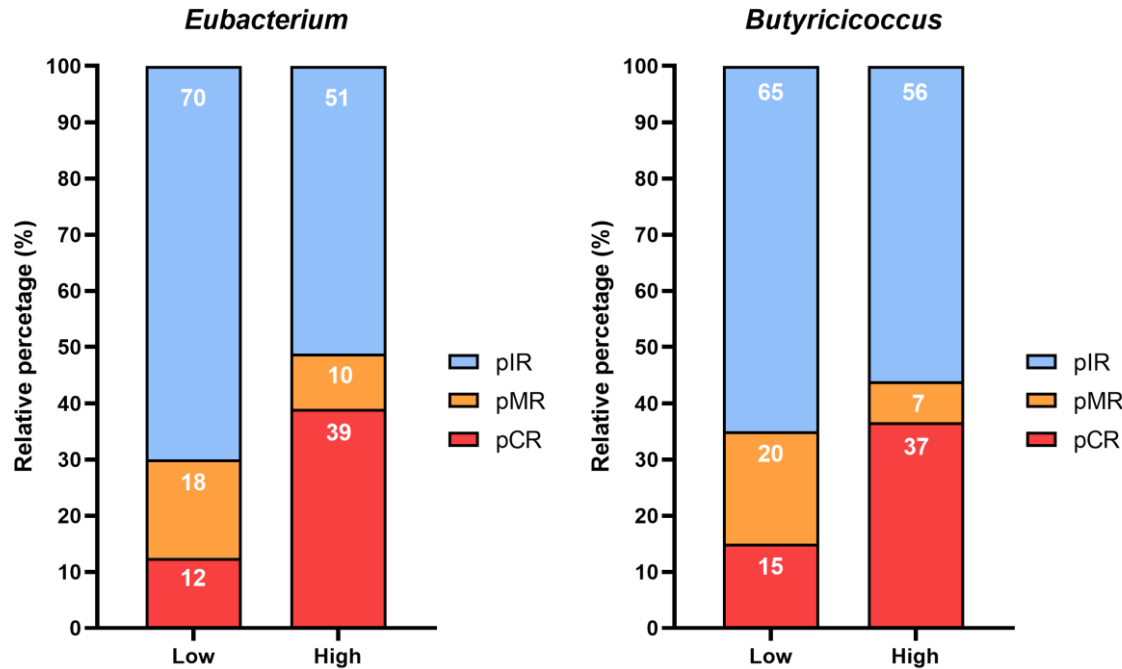


3. Resultados

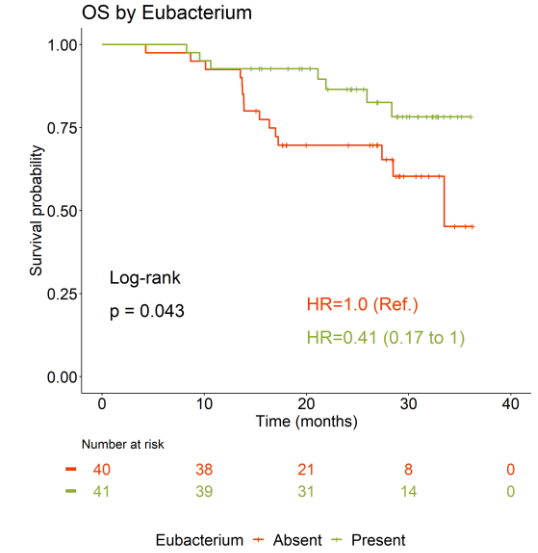
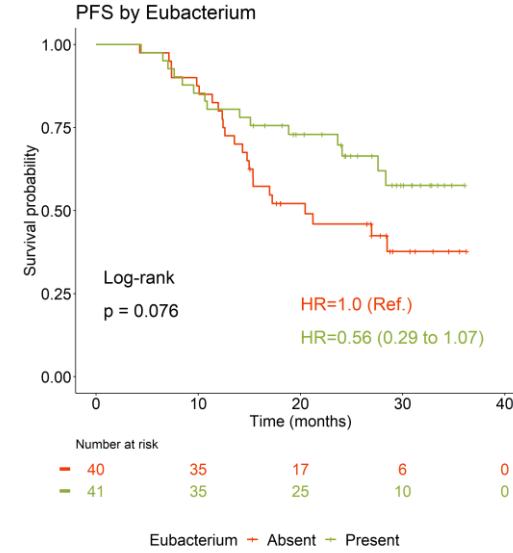
3.3 – Asociación a respuesta patológica y supervivencia



Respuesta patológica completa (pCR)



Supervivencia libre de progresión (PFS) / supervivencia global (SG)

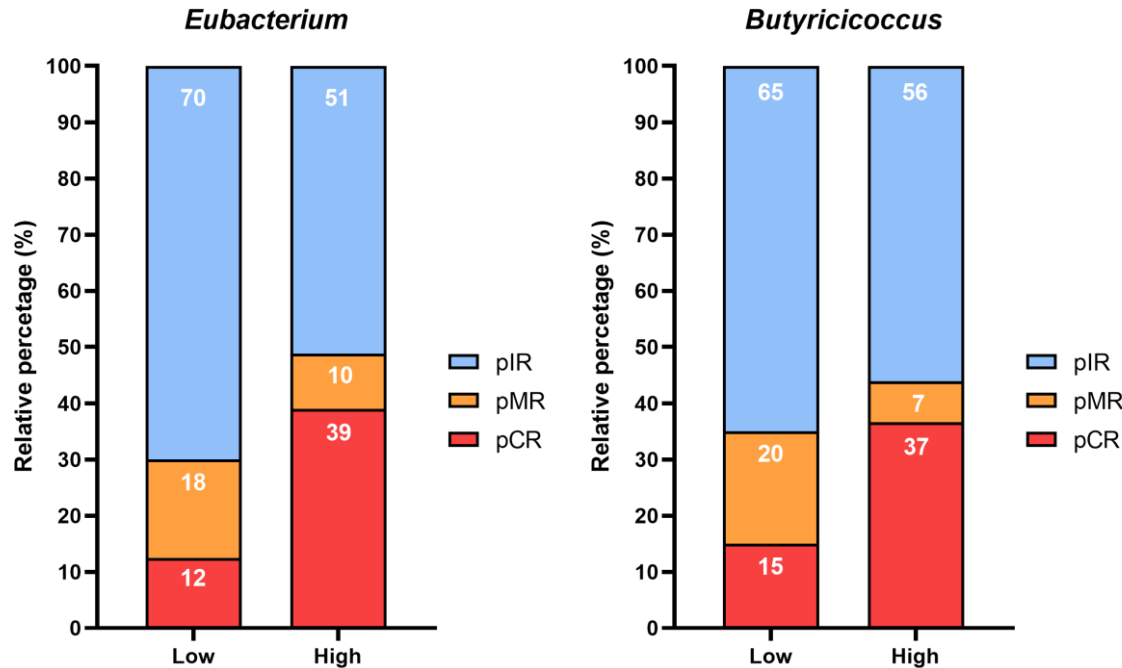


3. Resultados

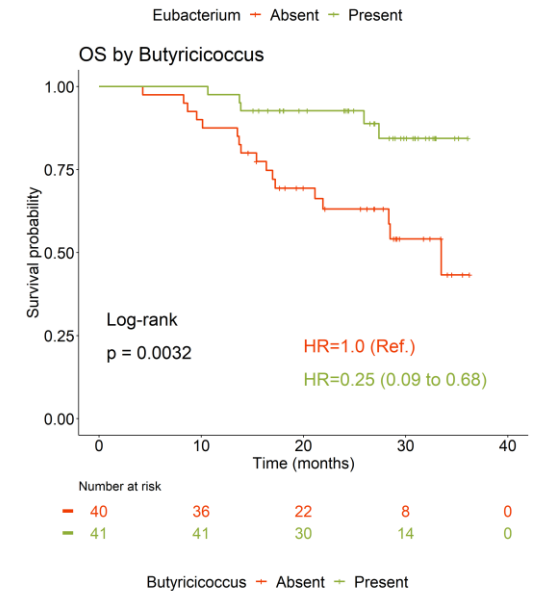
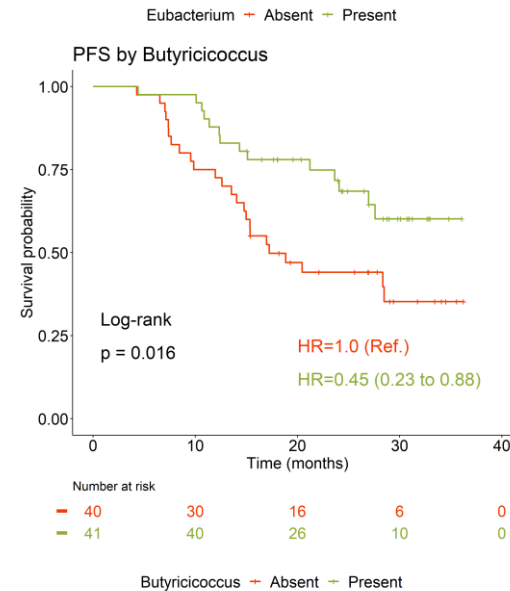
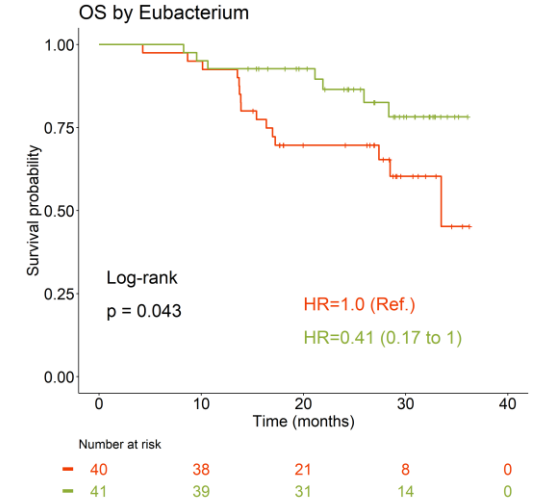
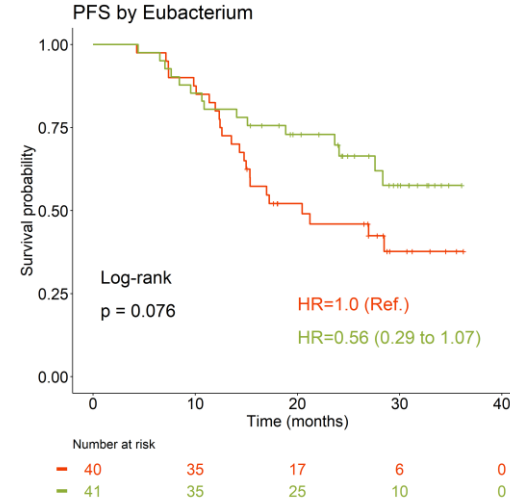
3.3 – Asociación a respuesta patológica y supervivencia



Respuesta patológica completa (pCR)



Supervivencia libre de progresión (PFS) / supervivencia global (SG)

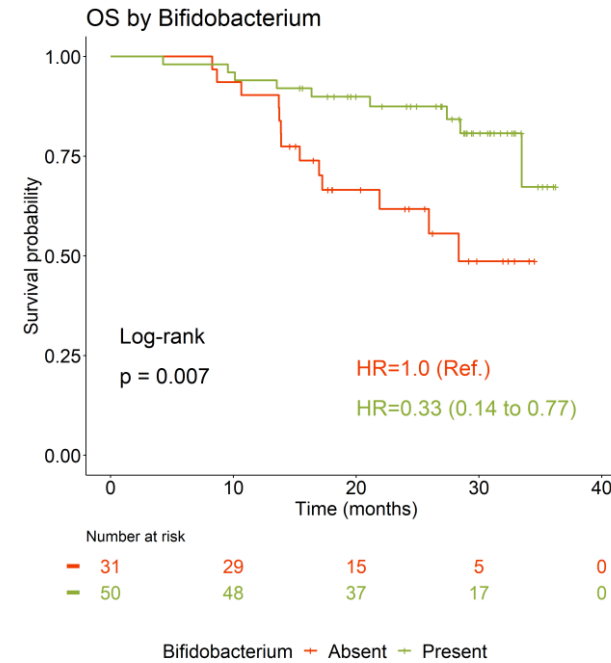
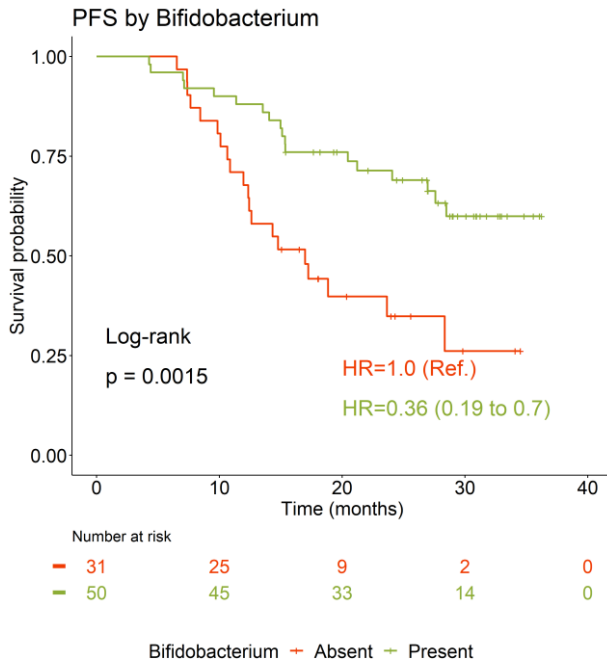


3. Resultados

3.3 – Asociación a respuesta patológica y supervivencia



Supervivencia libre de progresión (PFS) / supervivencia global (SG)

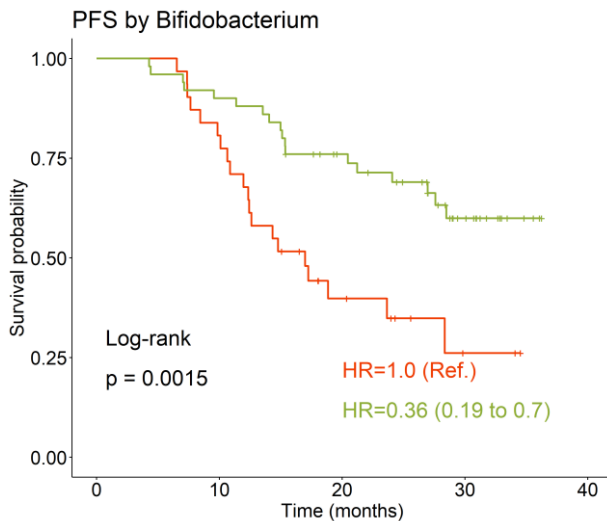


3. Resultados

3.3 – Asociación a respuesta patológica y supervivencia

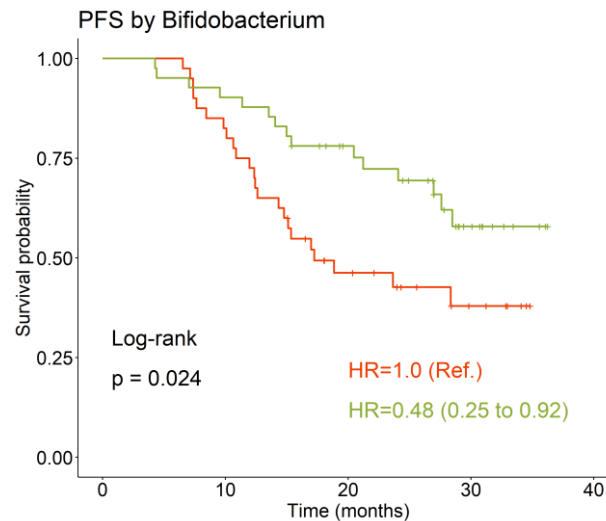


Supervivencia libre de progresión (PFS) / supervivencia global (SG)



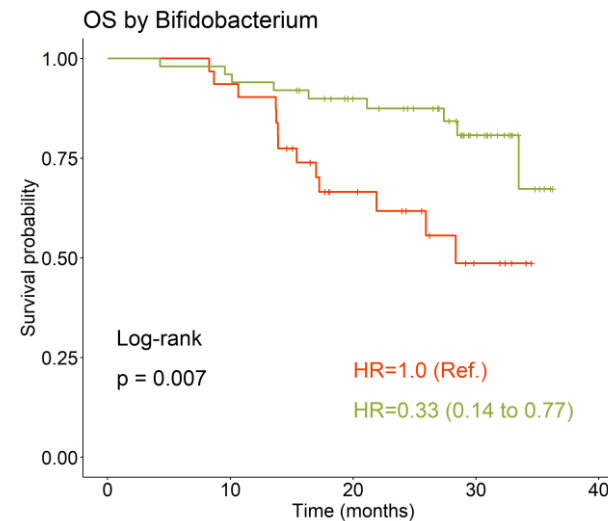
Number at risk					
Time (months)	0	10	20	30	40
Absent (Red)	31	25	9	2	0
Present (Green)	50	45	33	14	0

Bifidobacterium + Absent + Present



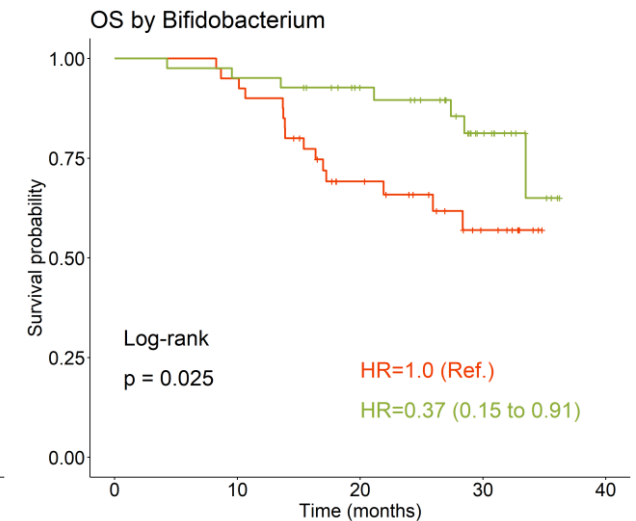
Number at risk					
Time (months)	0	10	20	30	40
Below mean (Red)	40	33	15	6	0
Above mean (Green)	41	37	27	10	0

Bifidobacterium + Below mean + Above mean



Number at risk					
Time (months)	0	10	20	30	40
Absent (Red)	31	29	15	5	0
Present (Green)	50	48	37	17	0

Bifidobacterium + Absent + Present



Number at risk					
Time (months)	0	10	20	30	40
Below mean (Red)	40	38	22	9	0
Above mean (Green)	41	39	30	13	0

Bifidobacterium + Below mean + Above mean

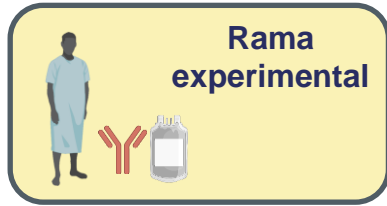


3. Resultados

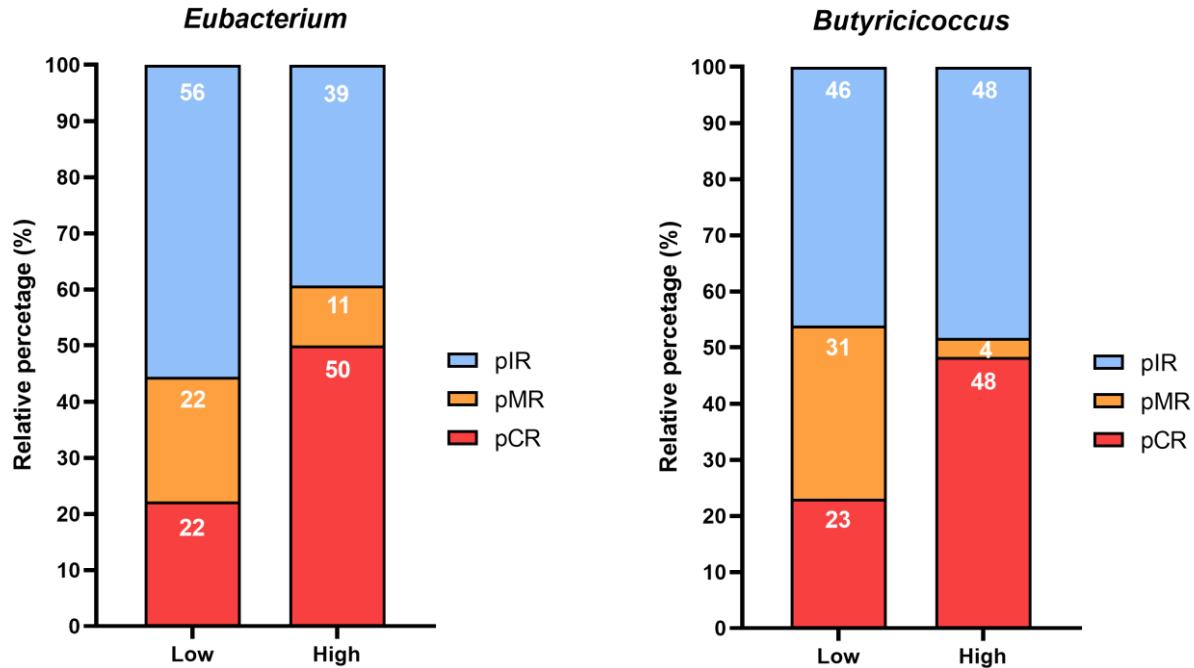
3.3 – Asociación a supervivencia libre de progresión y global

3. Resultados

3.3 – Asociación a supervivencia libre de progresión y global

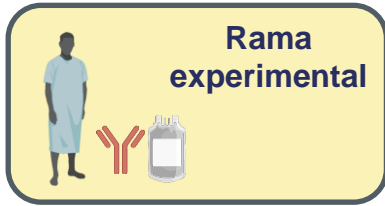


Respuesta patológica completa (pCR)

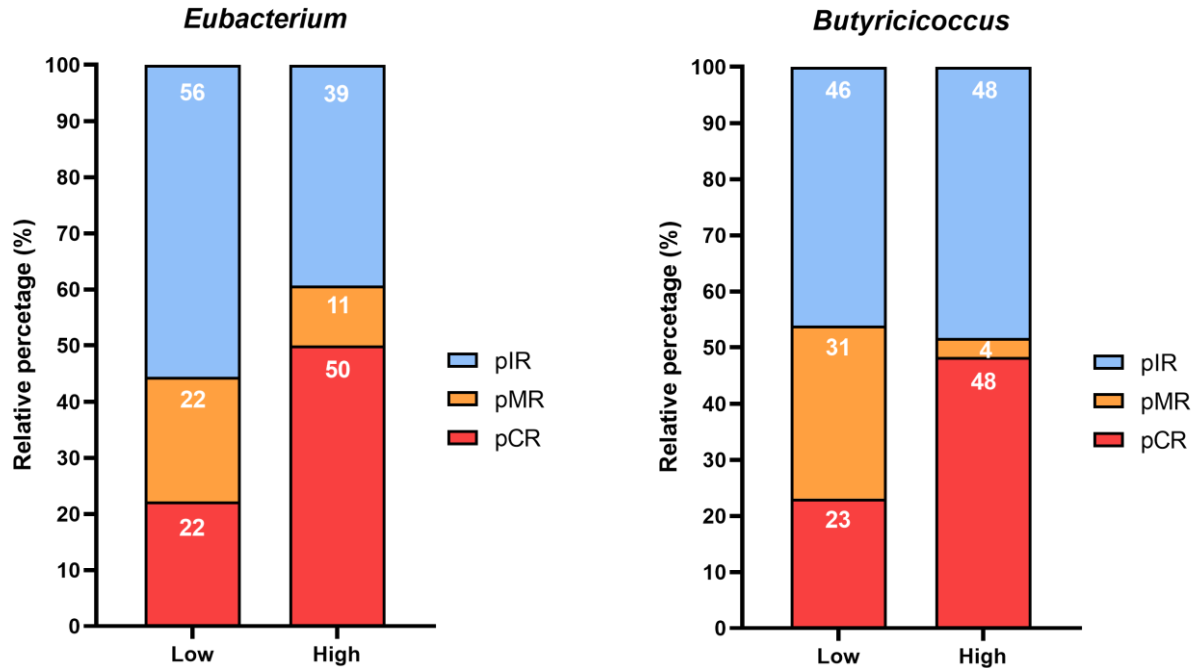


3. Resultados

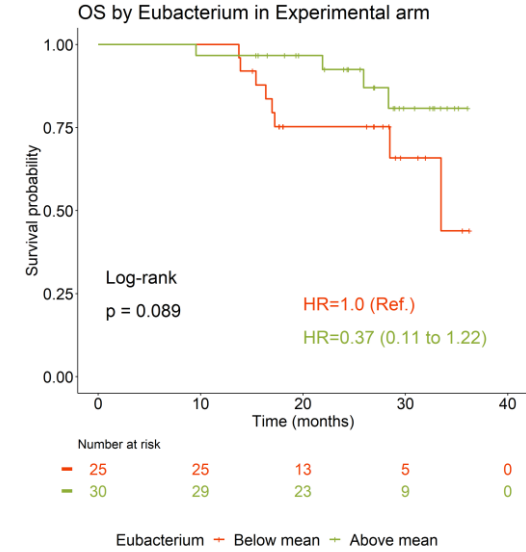
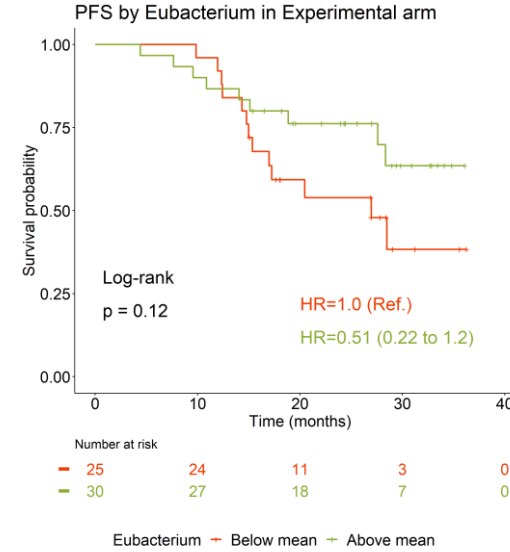
3.3 – Asociación a supervivencia libre de progresión y global



Respuesta patológica completa (pCR)

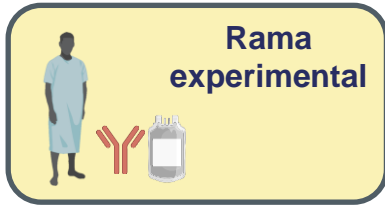


Supervivencia libre de progresión (PFS) / supervivencia global (SG)

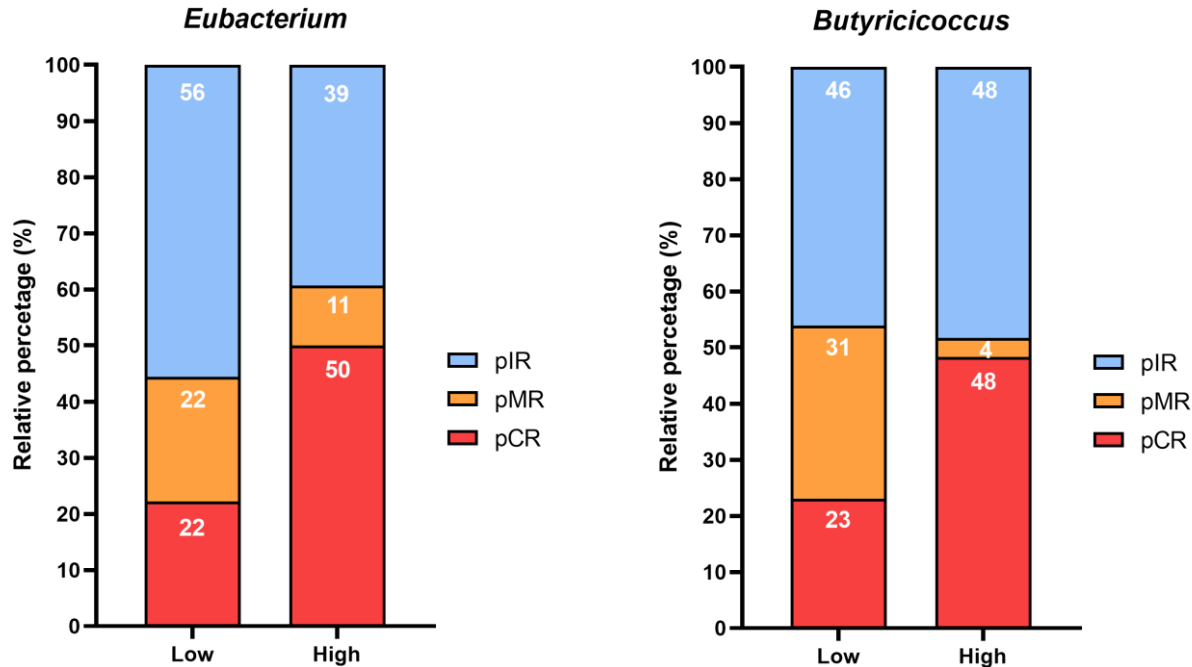


3. Resultados

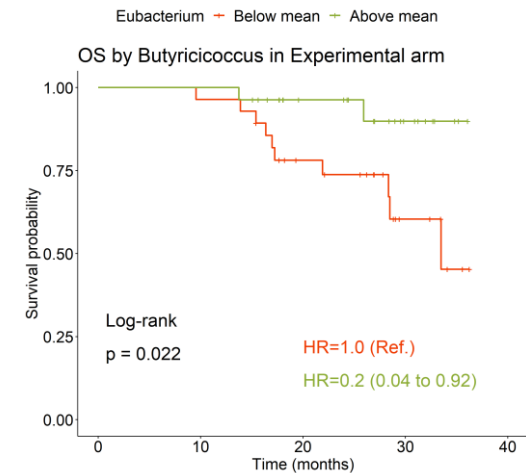
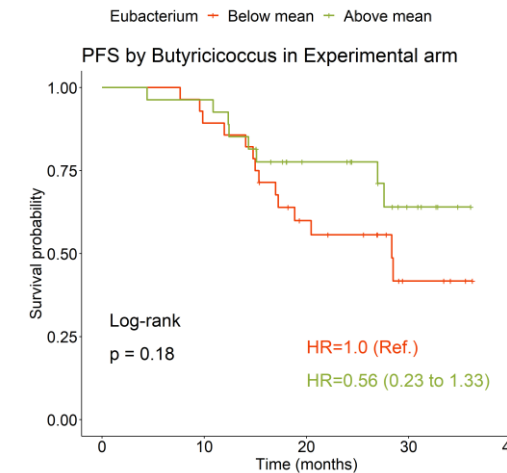
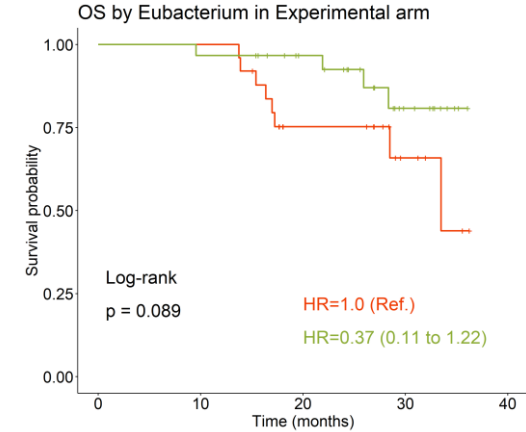
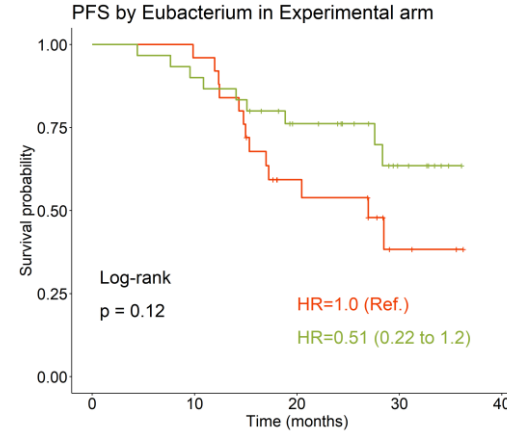
3.3 – Asociación a supervivencia libre de progresión y global



Respuesta patológica completa (pCR)



Supervivencia libre de progresión (PFS) / supervivencia global (SG)

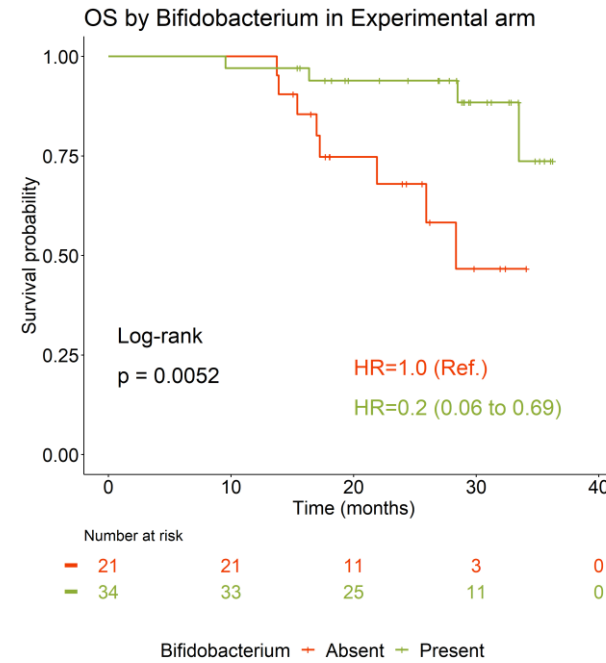
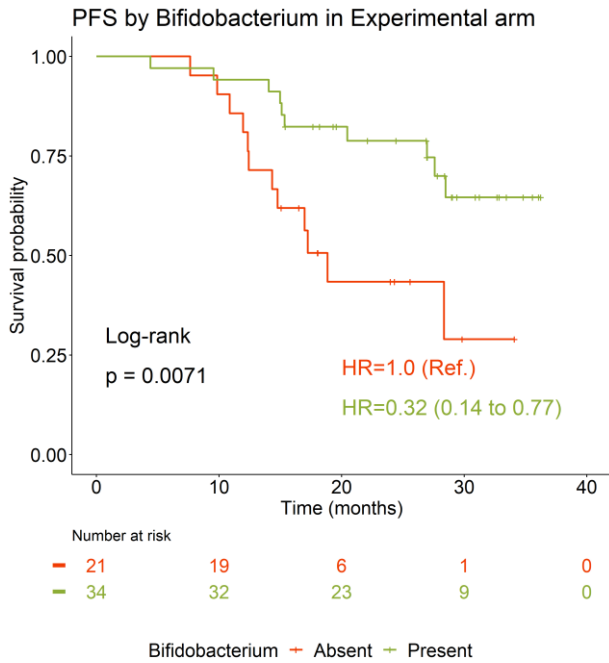


3. Resultados

3.3 – Asociación a supervivencia libre de progresión y global



Supervivencia libre de progresión (PFS) / supervivencia global (SG)

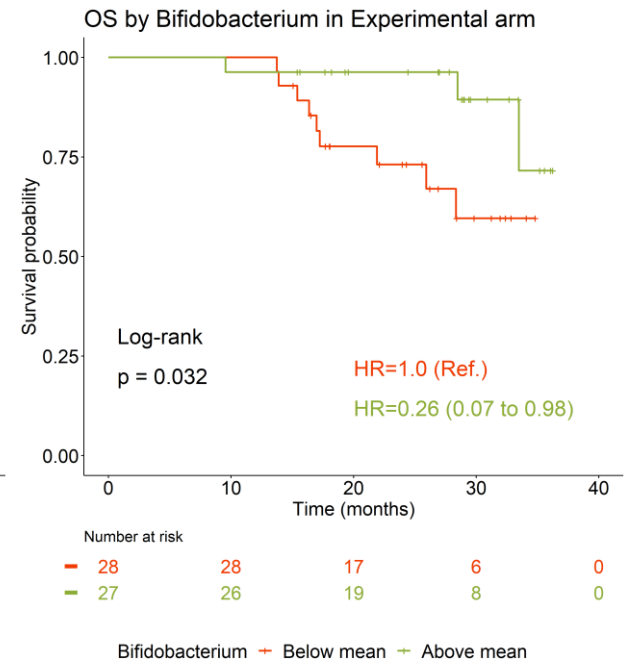
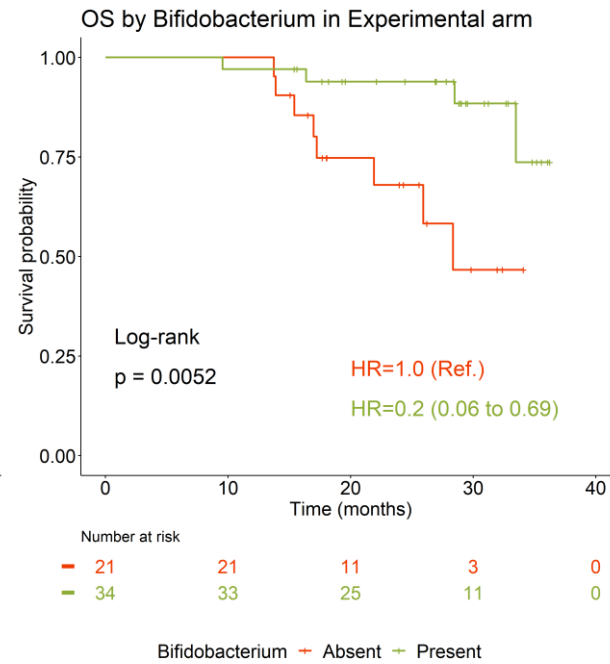
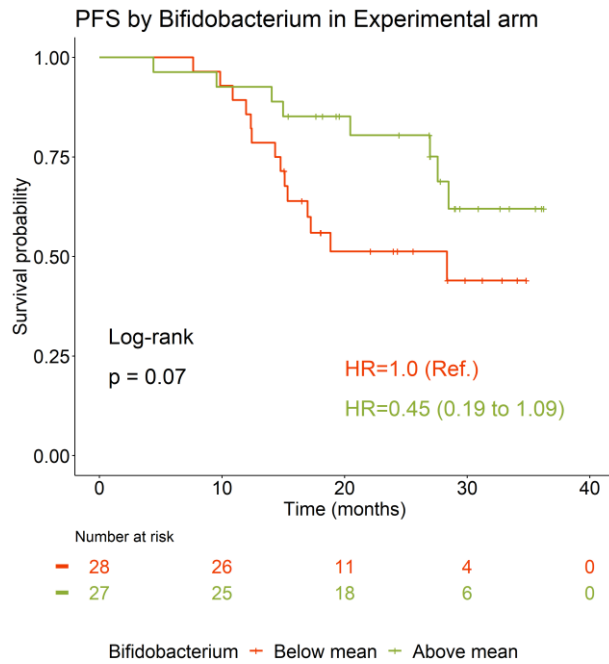
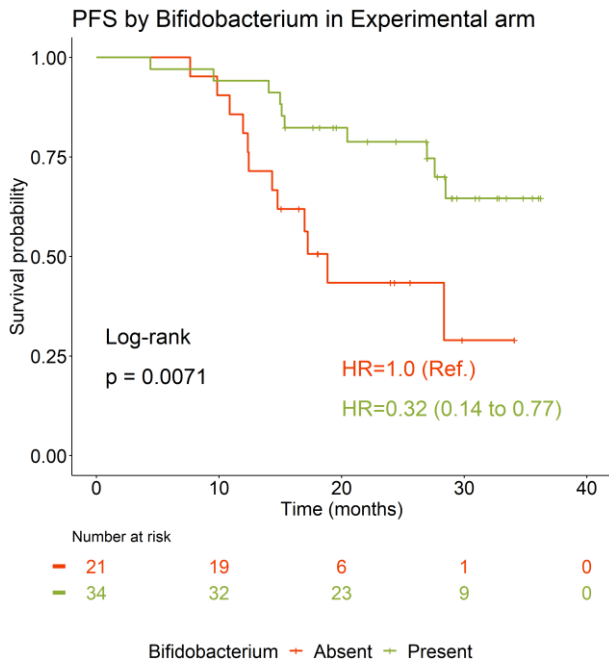


3. Resultados

3.3 – Asociación a supervivencia libre de progresión y global



Supervivencia libre de progresión (PFS) / supervivencia global (SG)



3. Resultados

3.3 – Asociación a supervivencia libre de progresión y global

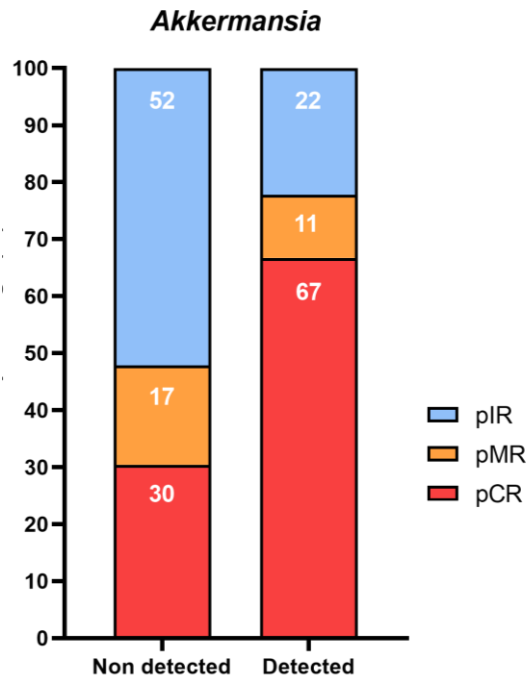


3. Resultados

3.3 – Asociación a supervivencia libre de progresión y global



Respuesta patológica completa (pCR)

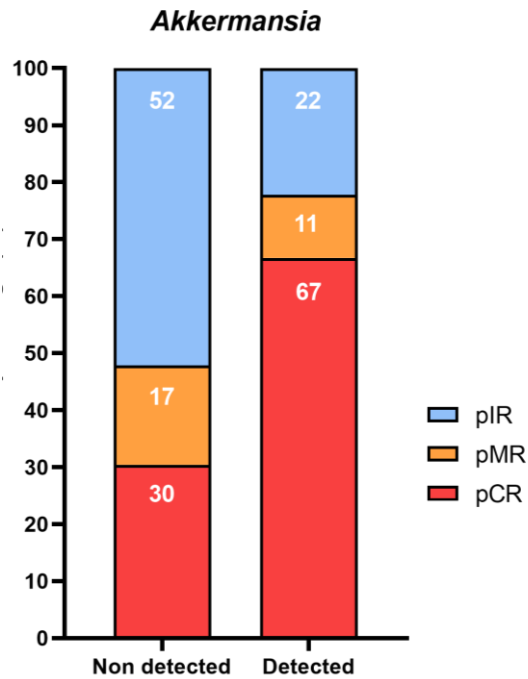


3. Resultados

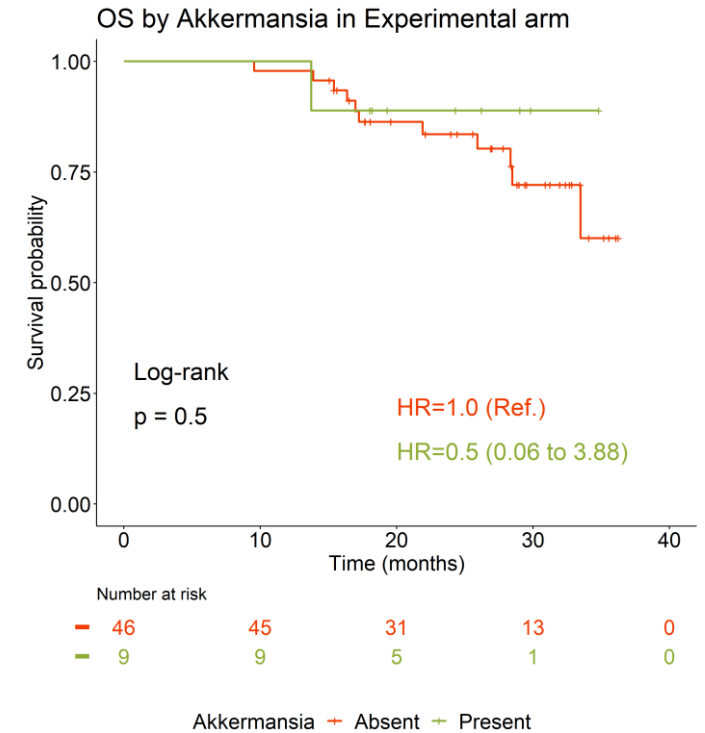
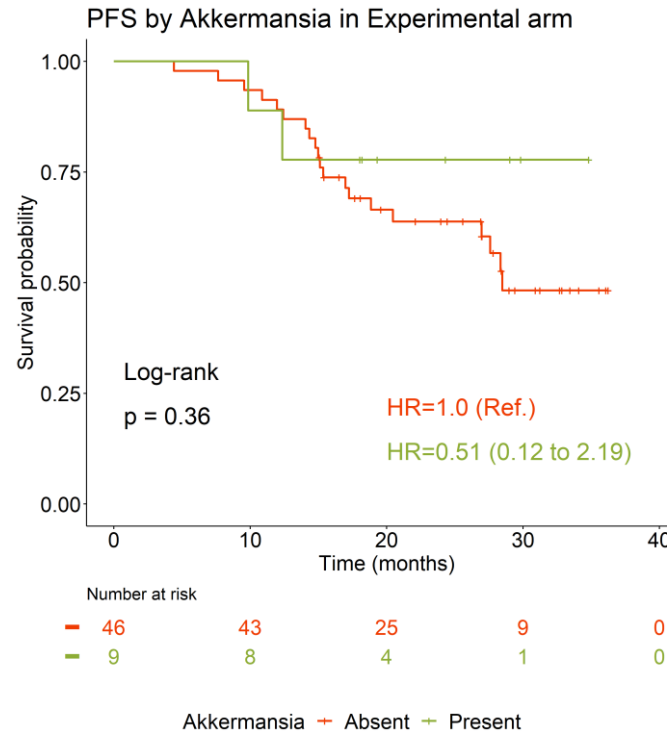
3.3 – Asociación a supervivencia libre de progresión y global



Respuesta patológica completa (pCR)



Supervivencia libre de progresión (PFS) / supervivencia global (SG)





3. Resultados

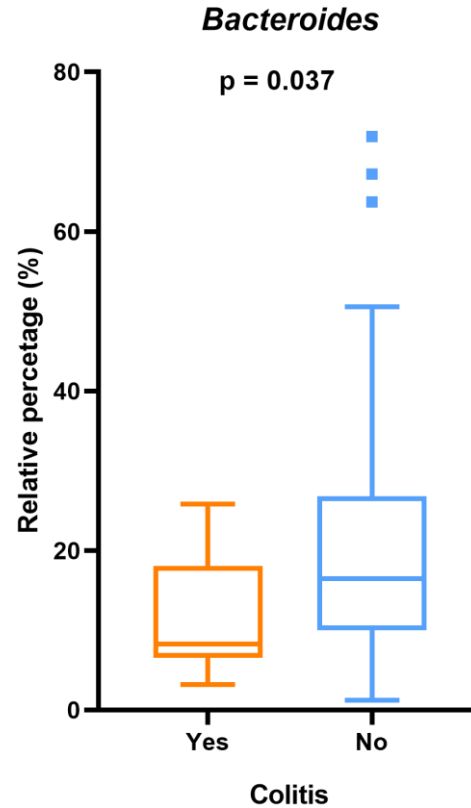
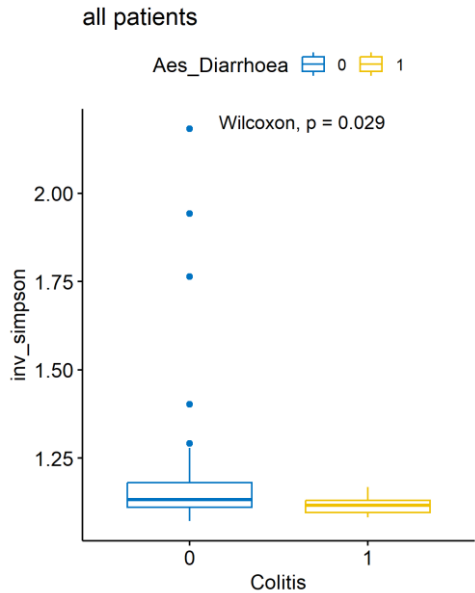
3.4 – Asociación a eventos adversos de colitis

	N = 81
Eventos adversos colitis, n (%)	25 (30,9)
Pacientes afectados n (%)	18 (22,2)
Grado 2	4 (4,9)
Grado 3	2 (2,5)

3. Resultados

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4. Conclusiones

- La diversidad de la microbiota intestinal, en especial la riqueza de especies, parece tener un impacto en la supervivencia libre de progresión de los pacientes tratados con inmunoterapia más quimioterapia y especialmente en aquellos tratados con quimioterapia.
- La composición de la microbiota intestinal puede jugar un papel en la respuesta a la inmunoterapia en combinación con quimioterapia en la estrategia de tratamiento neoadyuvante en pacientes localmente avanzados con CPCNP resecables.
- La composición de la microbiota intestinal puede asociarse a eventos adversos de colitis.

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¡Muchas Gracias!