XIX JORNADA DE ACTUALIZACIÓN ASCO GI 2025

5 de marzo de 2025

¿Qué hay de nuevo en los tumores colorrectales?

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Speaking:MSD,BMS, Servier, Amgen, Lilly, Incyte,Roche,Astra Zeneca,Takeda,Beigene

Índice

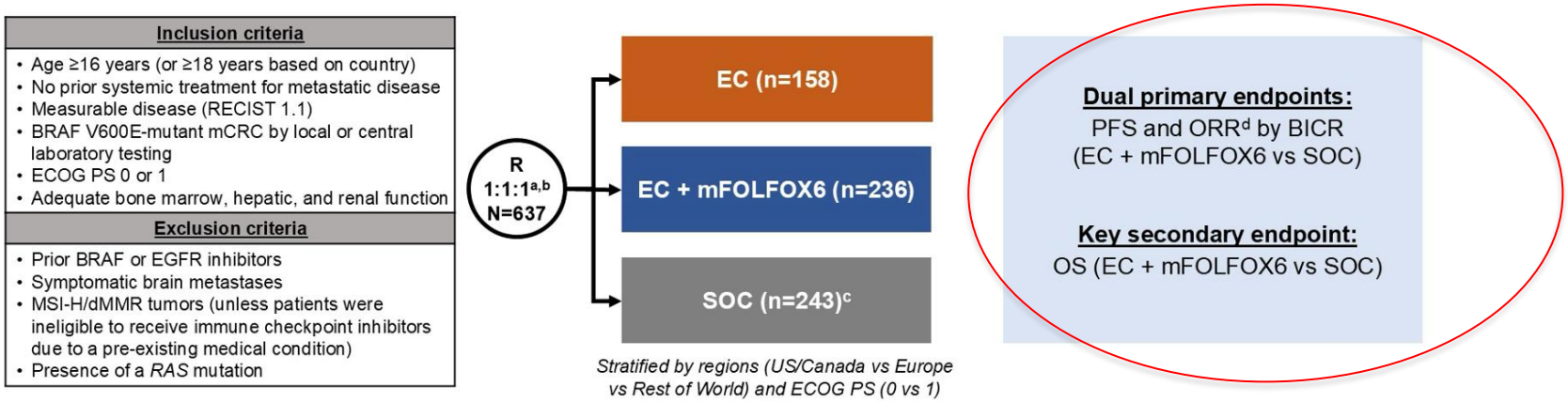
- Tratamiento dirigido por biomarcador en 1L
- Biopsia Líquida en Enfermedad Localizada
- Colon Refractario
- Colon Localizado

BLOQUE I

TRATAMIENTOS DIRIGIDOS POR BIOMARCADOR EN 1L

Tratamientos 1L BRAF^{mutado}

BREAKWATER: Diseño

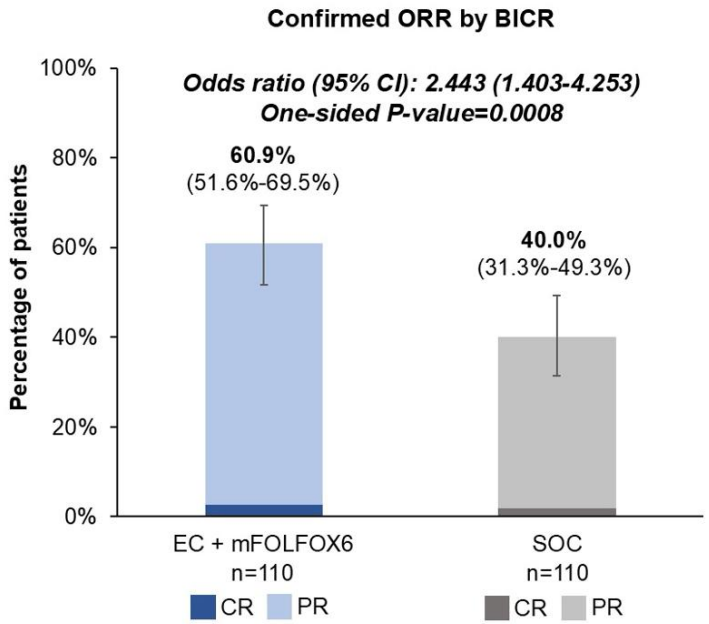


Here we present the primary analysis of ORR by BICR (one of the dual primary endpoints), an interim analysis of OS, and safety in the EC + mFOLFOX6 and SOC arms

Kopetz et al. ASCOGI2025.Abstract16

Tratamientos 1L BRAF^{mutado}

BREAKWATER: Resultados (Sgmto 10 meses)



Confirmed Best Overall Response, TTR, and DOR by BICR

	EC + mFOLFOX6 n=110	SOC n=110
Confirmed best overall response, n (%)		
CR	3 (2.7)	2 (1.8)
PR	64 (58.2)	42 (38.2)
SD	31 (28.2)	34 (30.9)
Non-CR/non-PD	3 (2.7)	4 (3.6)
PD	3 (2.7)	9 (8.2)
NE	6 (5.5)	19 (17.3)
	n=67	**n=44**
TTR, median (range), weeks	7.1 (5.7-53.7)	7.3 (5.4-48.0)
Estimated DOR, median (range), months	13.9 (8.5-NE)	11.1 (6.7-12.7)
Patients with a DOR of ≥6 months, n (%)	46 (68.7)	15 (34.1)
Patients with a DOR of ≥12 months, n (%)	15 (22.4)	5 (11.4)

x2

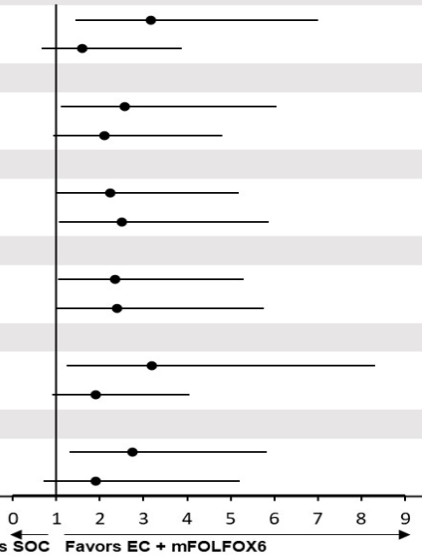
Kopetz et al. ASCOGI2025.Abstract16

Tratamientos 1L BRAF^{mutado}

BREAKWATER: Resultados (Sgmto 10 meses)

Subgroup Analysis of ORR by BICR

	Number of responders/ Number of patients		ORR (%)		Odds ratio (95% CI)
	EC + mFOLFOX6	SOC	EC + mFOLFOX6	SOC	
Age					
<65 years	41/64	22/61	64.1	36.1	3.160 (1.432-7.010)
≥65 years	26/46	22/49	56.5	44.9	1.595 (0.658-3.883)
Gender					
Male	36/57	20/50	63,2	40.0	2.571 (1.099-6.050)
Female	31/53	24/60	58.5	40.0	2.114 (0.934-4.803)
ECOG PS at baseline					
0	37/56	26/56	66.1	46.4	2.247 (0.981-5.178)
1	30/54	18/54	55.6	33.3	2.500 (1.070-5.880)
Number of organs involved at baseline per BICR					
≤2	32/58	20/58	55.2	34.5	2.338 (1.037-5.301)
≥3	35/52	24/52	67.3	46.2	2.402 (1.010-5.758)
Side of tumor					
Left	28/43	17/46	65.1	37.0	3.184 (1.232-8.313)
Right	39/67	27/64	58.2	42.2	1.909 (0.901-4.053)
Liver metastases at baseline per BICR					
Yes	47/69	31/71	68.1	43.7	2.757 (1.310-5.836)
No	20/41	13/39	48.8	33.3	1.905 (0.704-5.210)



Data cutoff: December 22, 2023.

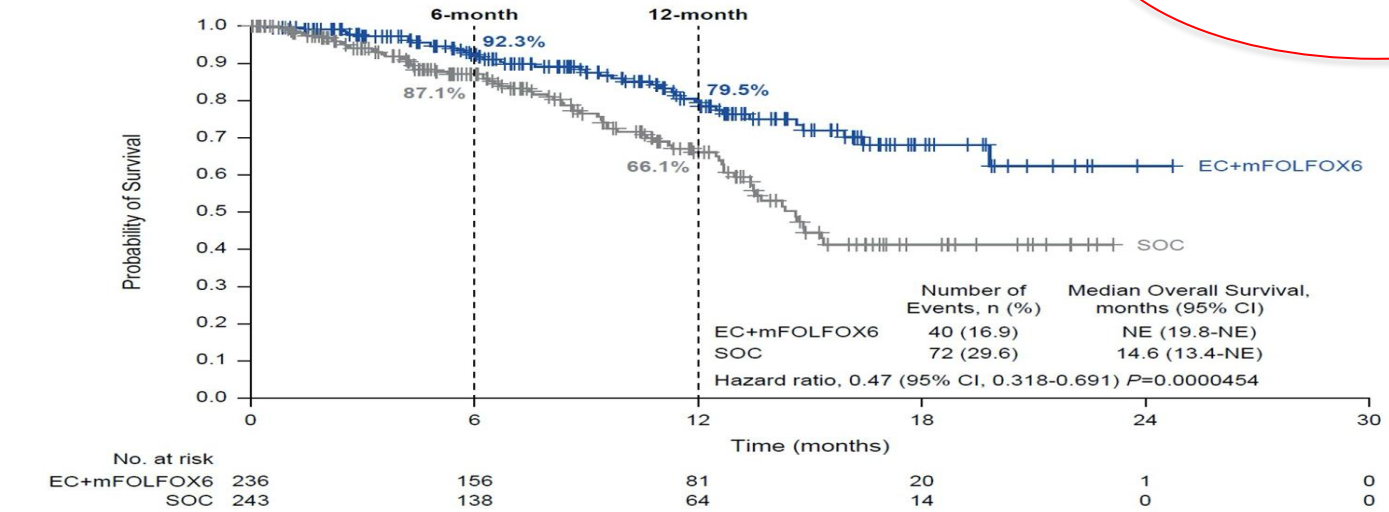
Kopetz et al. ASCOGI2025.Abstract16

Tratamientos 1L BRAF^{mutado}

BREAKWATER: Resultados (Sgmto 10 meses)

No alcanza p preespecificada

Interim Overall Survival[a]



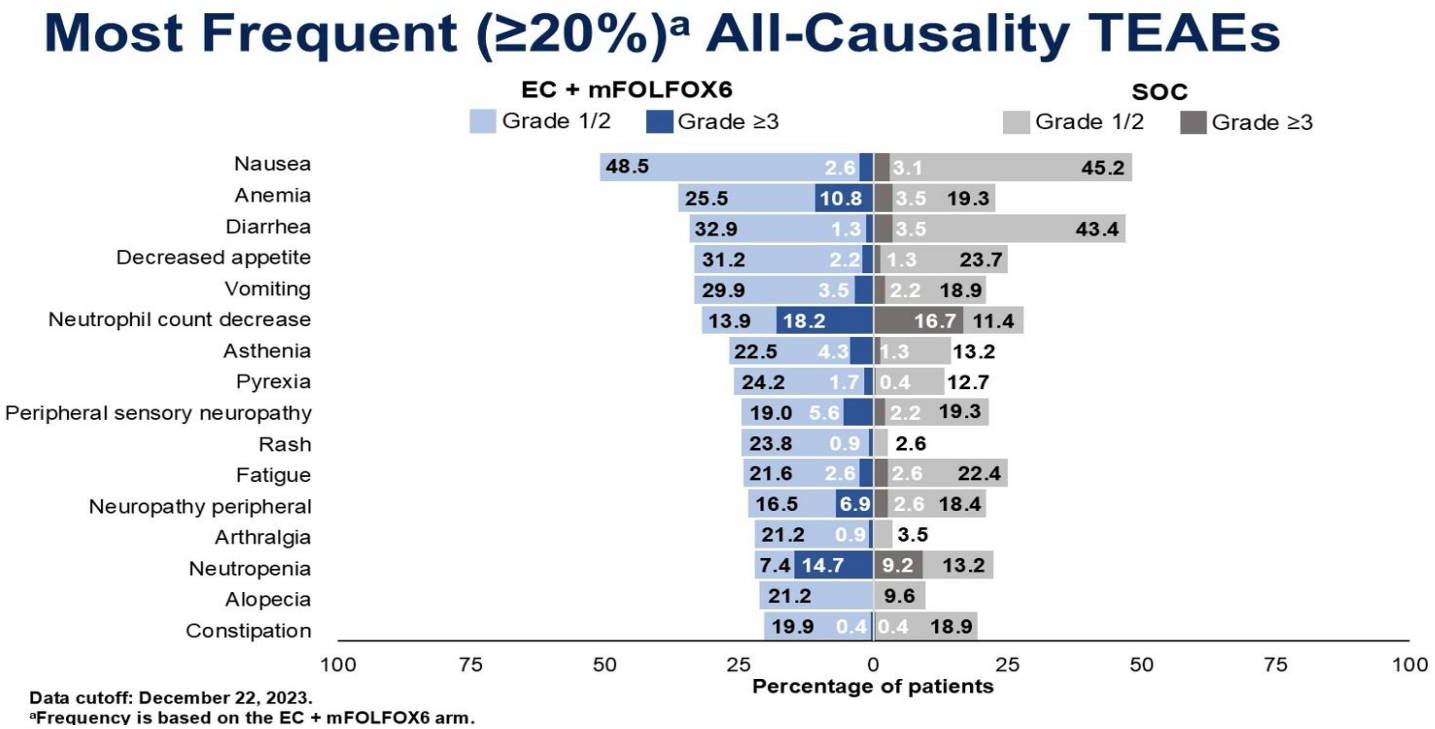
Data cutoff: December 22, 2023.

[a]OS was tested following the prespecified plan with one-sided alpha of 0.000000083, calculated as a portion of the nominal one-sided alpha of 0.001. Statistical significance was not achieved at this time.

Kopetz et al. ASCOGI2025.Abstract16

Tratamientos 1L BRAF^{mutado}

BREAKWATER: Efectos adversos

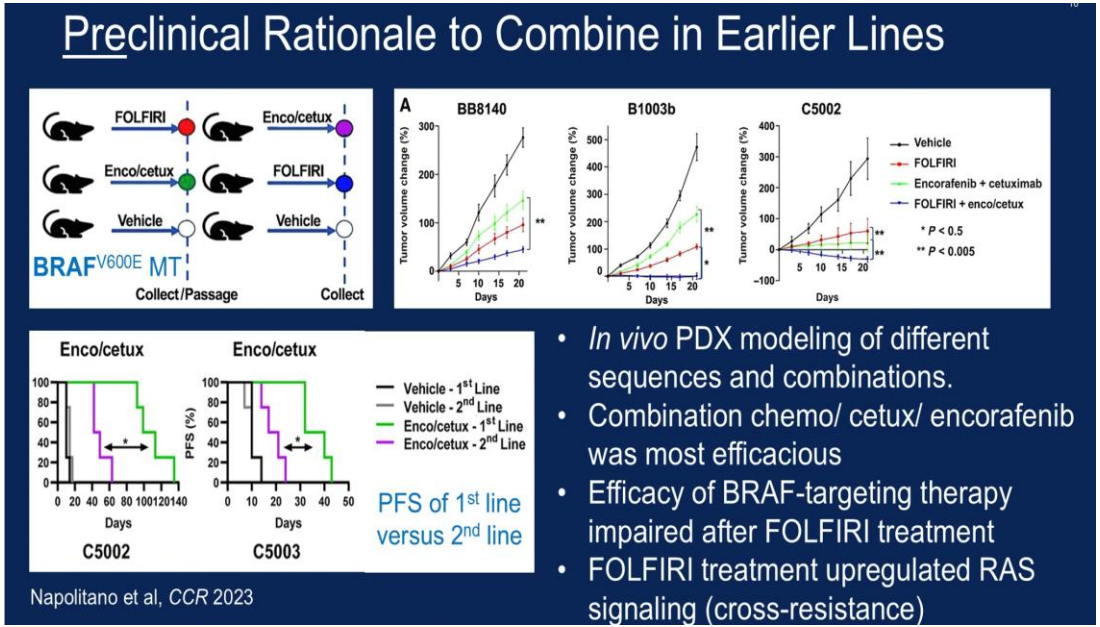


Kopetz et al. ASCOGI2025.Abstract16

CONTEXTUALIZACIÓN

Ttos frente a BRAF ¿los movemos a 1L?

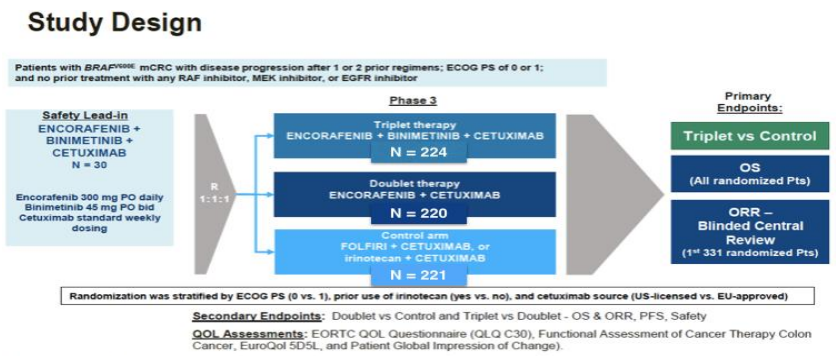
1. Aumento TR (60% vs 40%), sin aún ver aumento en SG y con toxicidad manejable
2. Ofrece un acceso precoz a tto dirigido.
3. Vemos mejor los Eadv (menos ef.adv relacionados con evolución de la enfermedad)
4. N de pacientes amplio.
5. "The sooner the best"

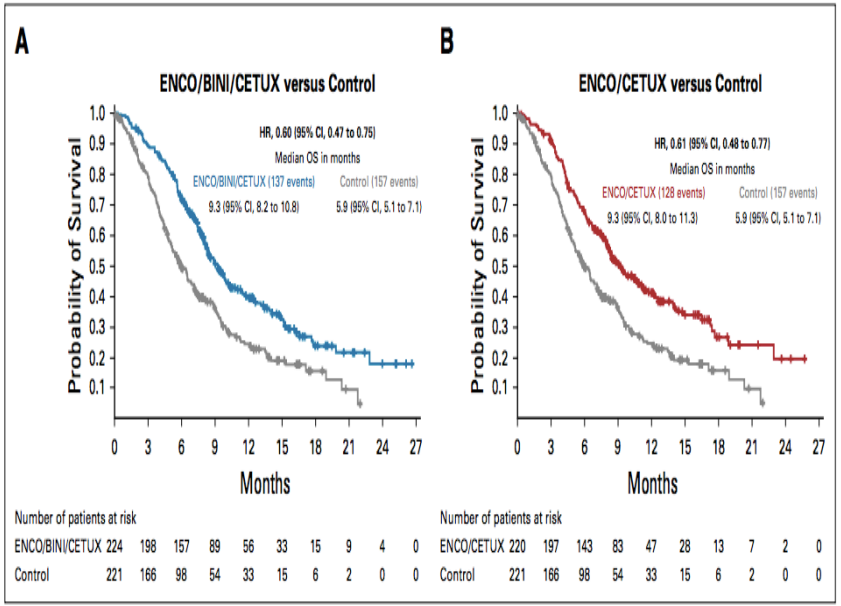


CONTEXTUALIZACIÓN

Ttos frente a BRAF ¿los movemos a 1L?

1.Solo BRAF V600E
2.Desconocemos el papel de mantener tto dirigido a PE
3. Problemente desplazaremos a BEACON

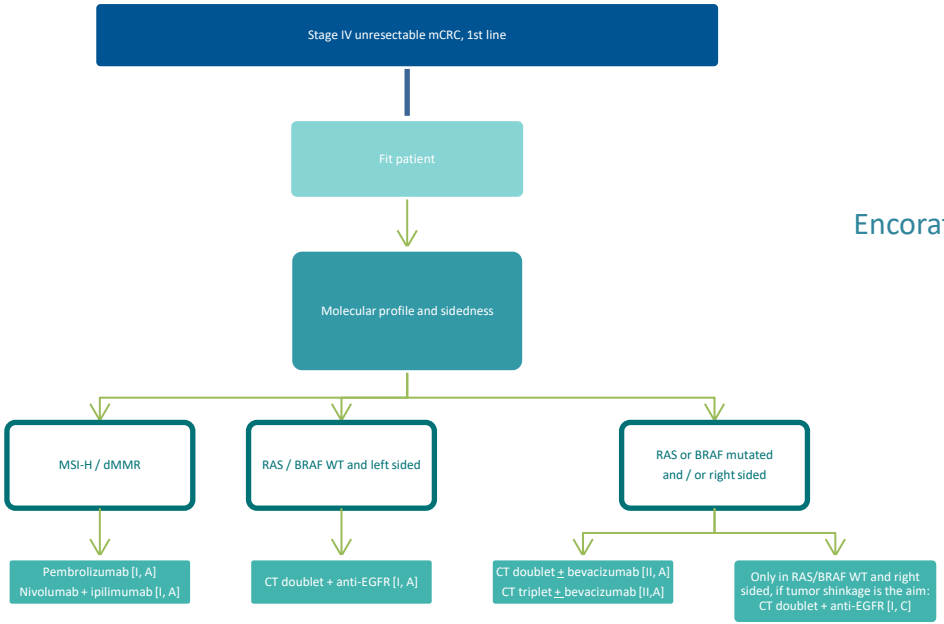




Tabernero J. J Clin Oncol 2021; 39:273-284

CONTEXTUALIZACIÓN

Ttos frente a BRAF ¿los movemos a 1L?



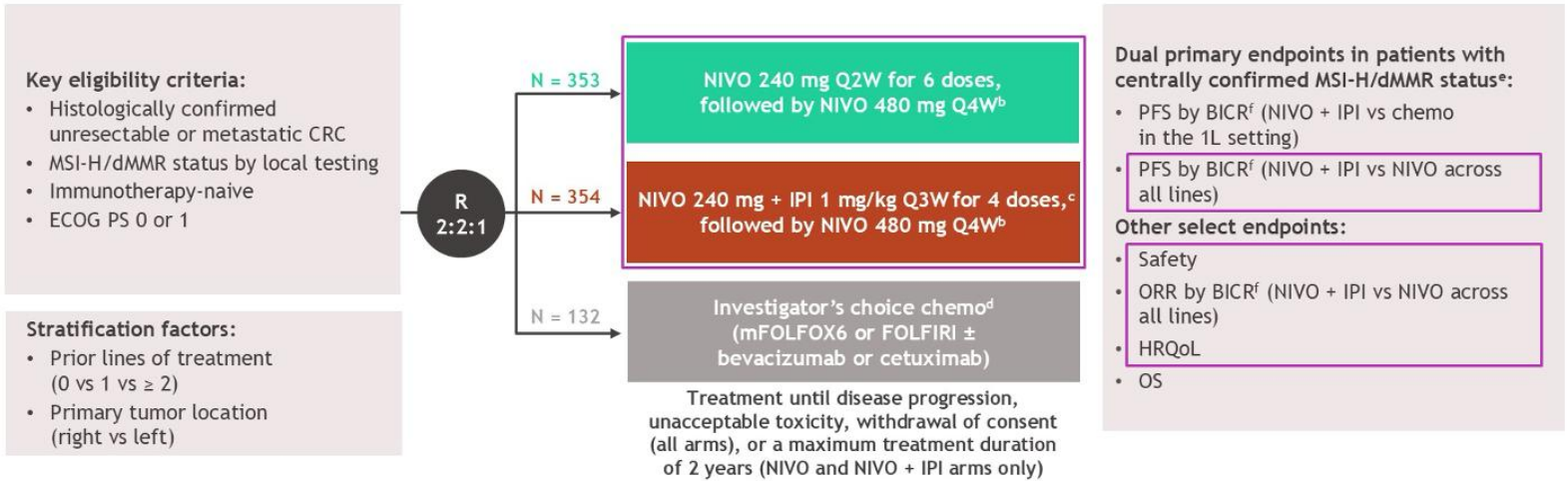
BRAF V600E ^{mt}

Encorafenib/cetuximab and FOLFOX

SEOM Living Guidelines 2025

Tratamientos 1L **MSI-H**

8HW: Diseño



- At data cutoff (August 28, 2024), the median follow-up[g] was 47.0 months (range, 16.7-60.5)

Seguimiento 4 años

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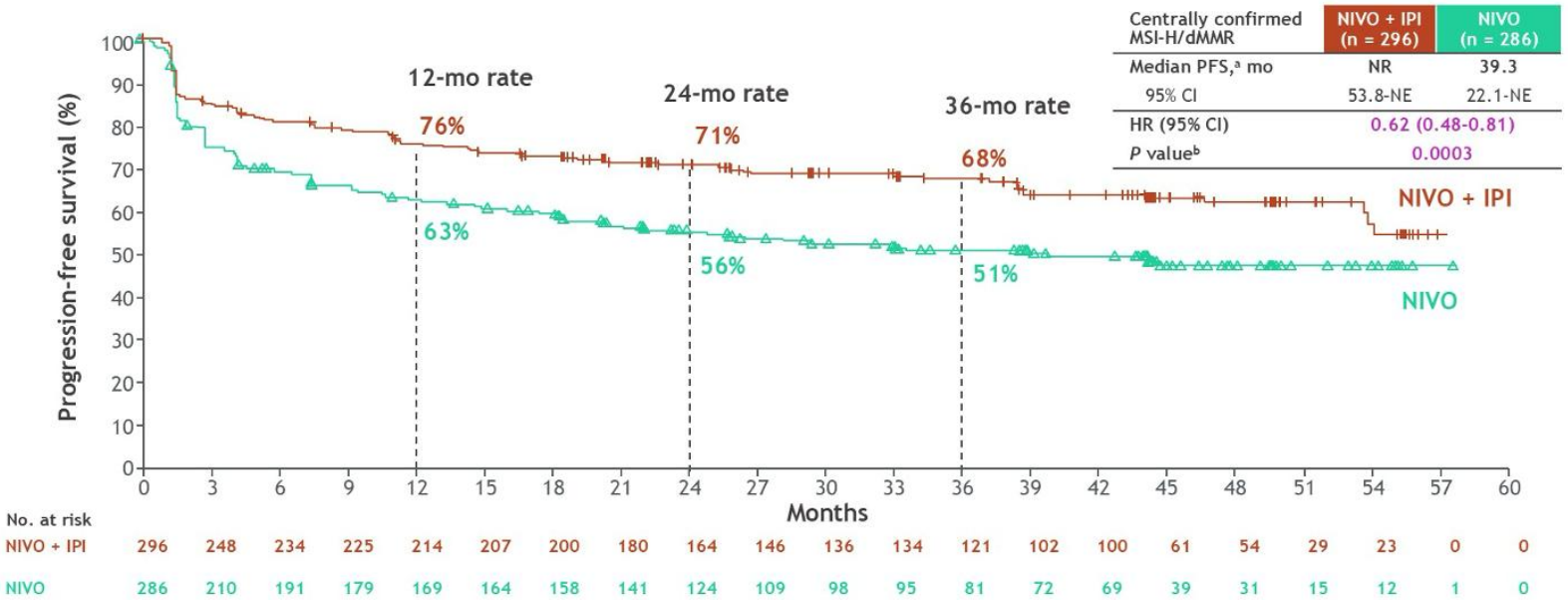
Tratamientos 1L **MSI-H**

8HW: Resultado SLP



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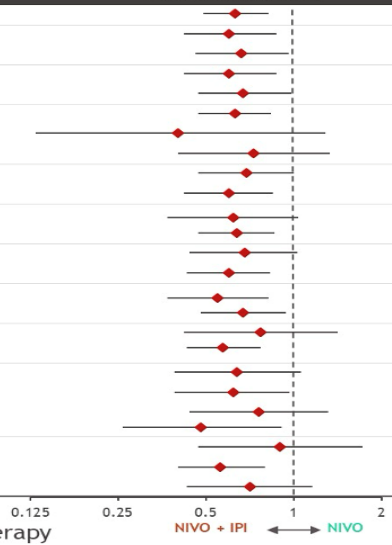
Tratamientos 1L **MSI-H**

8HW: Resultado SLP subgrupos

Category (centrally confirmed MSI-H/dMMR)	Subgroup	Median PFS,[a] mo		Unstratified HR	Unstratified HR (95% CI)
		NIVO + IPI	NIVO		
Overall (N = 582)		NR	39.3	0.63	
Age, years	< 65 (n = 321)	NR	NR	0.60	
	≥ 65 (n = 261)	NR	29.4	0.66	
Sex	Male (n = 284)	NR	28.2	0.60	
	Female (n = 298)	NR	NR	0.67	
Region	US/Canada/Europe (n = 415)	NR	29.4	0.63	
	Asia (n = 52)	NR	NR	0.40	
	Rest of world (n = 115)	NR	NR	0.73	
ECOG PS	0 (n = 313)	54.1	NR	0.69	
	1 (n = 269)	NR	18.2	0.60	
Tumor sidedness	Left (n = 152)	NR	NR	0.62	
	Right (n = 430)	NR	33.2	0.64	
Liver metastases[a,b]	Yes (n = 210)	NR	NR	0.68	
	No (n = 368)	NR	33.2	0.60	
Peritoneal metastases[a,b]	Yes (n = 226)	54.1	24.8	0.55	
	No (n = 352)	NR	NR	0.67	
Tumor cell PD-L1 expression	≥ 1% (n = 133)	NR	NR	0.77	
	< 1% (n = 427)	NR	24.8	0.57	
BRAF/KRAS/NRAS mutation status	*BRAF/KRAS/NRAS* all wild type (n = 156)	NR	44.3	0.64	
	BRAF mutant (n = 179)	NR	25.9	0.62	
	KRAS or *NRAS* mutant (n = 125)	NR	NR	0.76	
	Unknown (n = 114)	54.1	38.1	0.48	
Clinical history of Lynch syndrome	Yes (n = 83)	53.8	38.1	0.90	
	No (n = 334)	NR	44.3	0.56	
	Unknown (n = 156)	NR	33.2	0.71	



- PFS consistently favored NIVO + IPI vs NIVO in prespecified subgroups across all lines of therapy

[a]Per BICR. [b]Patients may have had more than one site of metastasis.

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Tratamientos 1L **MSI-H**

8HW: Respuesta

Centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 296)	NIVO (n = 286)
ORR,[a] % (95% CI)	**71 (65-76)**	**58 (52-64)**
Difference in ORR,[b] % (95% CI)	13 (5-21)	
P value[c]	0.0011	
Best overall response,[a,d] %		
Complete response	30	28
Partial response	40	30
Stable disease	14	19
Progressive disease	10	19
Median TTR (range),[a,e] mo	2.8 (1.2-44.5)	2.8 (1.2-29.5)
Median DOR (95% CI),[a,e] mo	NR (NE)	NR (NE)

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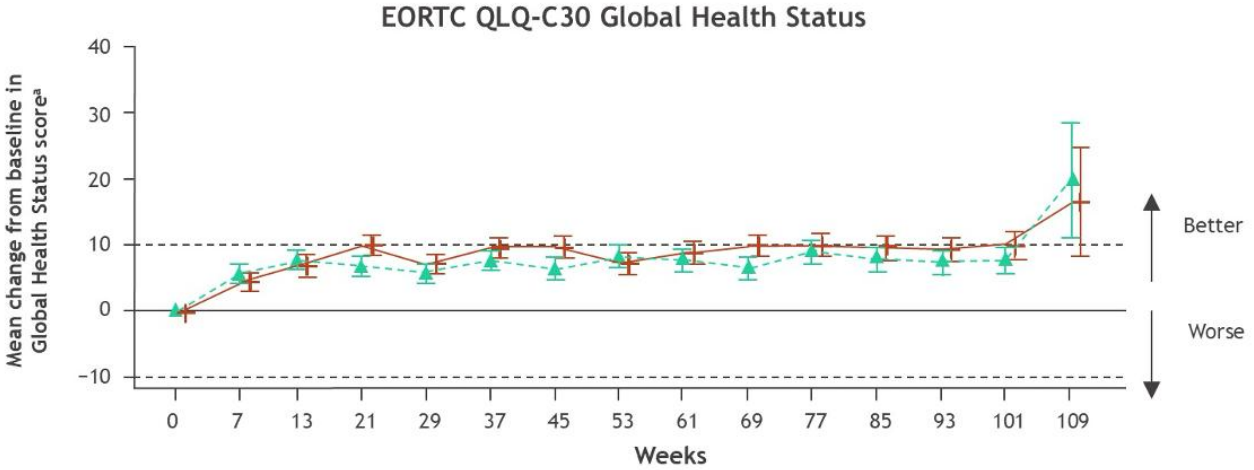
Tratamientos 1L **MSI-H**

8HW: Calidad de vida



- HRQoL improvements were observed with NIVO + IPI and NIVO in the EORTC QLQ-C30 Global Health Status subscale
  - Mean change from baseline scores were consistently positive in both arms, with the NIVO + IPI arm reaching the prespecified threshold for meaningful change from baseline starting at week 21

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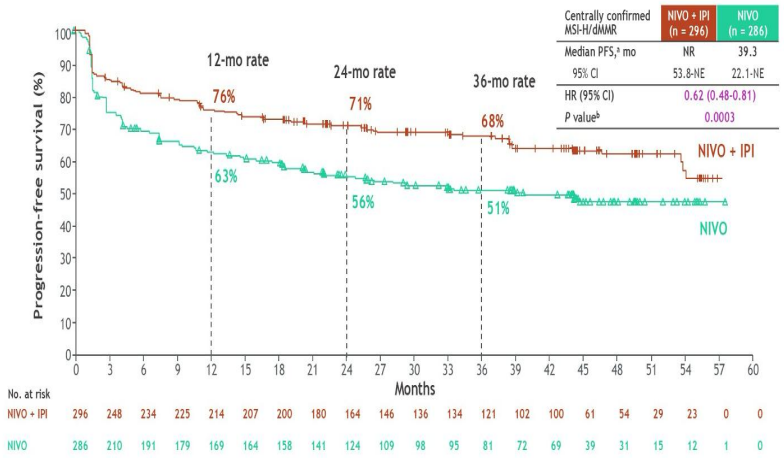
CONTEXTUALIZACIÓN

MSI-H ¿doblete o monoterapia?:Checkmate 8HW

1. Doble inhibición beneficio en mx hepáticas y peritoneales
2. Poco coste de toxicidad
3. Duda si añadir ipi a la PE y cuánto tiempo de IO



Andre et al. ASCOGI2025.LBA143

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	No (n = 352)	NR	NR	0.67	
Tumor cell PD-L1 expression	≥ 1% (n = 133)	NR	NR	0.77	
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BRAF/*KRAS*/*NRAS* mutation status	*BRAF*/*KRAS*/*NRAS* all wild type (n = 156)	NR	44.3	0.64	
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	Unknown (n = 114)	54.1	38.1	0.48	
Clinical history of Lynch syndrome	Yes (n = 83)	53.8	38.1	0.90	
	No (n = 334)	NR	44.3	0.56	
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CONTEXTUALIZACIÓN

MSI-H ¿doblete o monoterapia?:Checkmate 8HW

Factores Relacionados con el Paciente

Edad Avanzada

Mal PS por edad/comorbilidades

Riesgo EAirs

Factores Relacionados con el Tumor

Mal PS por alta carga de enfermedad

Marcadores de Inflamación sistémica (¿¿NLR altos??)

Ascitis /Mx hepáticas

Monoterapia

TR 43-58 %

Progresadores Precoces: 19% (8HW), 29%

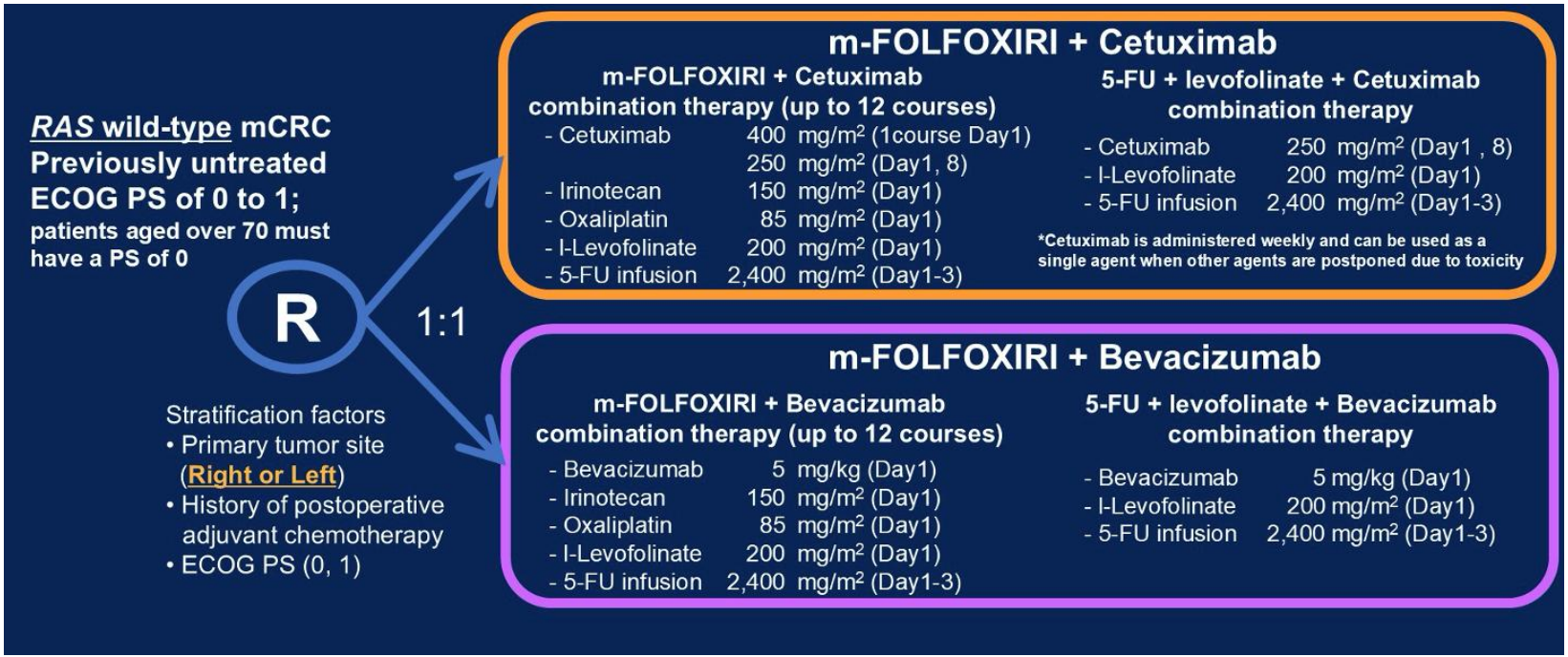
Dobletes

TR 71%%

Progresadores Precoces : <10%

Tratamientos 1L **RAS WT**

DEEPER: Diseño (Ojo RAS y estratifica por localización)



Obj.1:DpR

Tsuji et al. ASCOGI2025.Abtract17

Tratamientos 1L **RAS WT**

DEEPER: Objetivo 1º:DpR

Primary site	Left Side		Right Side	
	m-FOLFOXIRI + Bevacizumab (n=137)	m-FOLFOXIRI + Cetuximab (n=132)	m-FOLFOXIRI + Bevacizumab (n=25)	m-FOLFOXIRI + Cetuximab (n=27)
Median DpR(range)	**46.1% (3.2-100)**	**59.2% (-42.6-100)**	**41.2% (-0.6-85.6)**	**50.0% (-15.0-100)**
Mean (95% CI)	48.2% (44.9-51.5)	56.7% (52.2-61.2)	42.5% (32.1-52.9)	47.7% (37.3-58.1)
Standard deviation (95% CI)	19.55 (17.5-22.2)	26.00 (23.2-29.6)	25.17 (19.7-35.0)	26.19 (20.6-35.9)
Welch's t-test	*P*=0.0026		*P*=0.47	
Objective response rate (95% CI)	70.8% (63.2-78.4)	74.2% (66.8-81.7)	60.0% (40.8-79.2)	55.6% (36.8-74.3)
Chi-squared test	*P*=0.53		*P*=0.75	
Disease control rate (95% CI)	99.3% (97.8-100)	98.5% (96.4-100)	100.0% (100-100)	100.0% (100-100)
Chi-squared test	*P*=0.54		*P*=N/A	
R0 resection rate (95% CI)	23.4% (16.3-30.4)	28.8% (21.1-36.5)	8.0% (0-18.6)	14.8% (1.4-28.2)
Chi-squared test	*P*=0.31		*P*=0.44	

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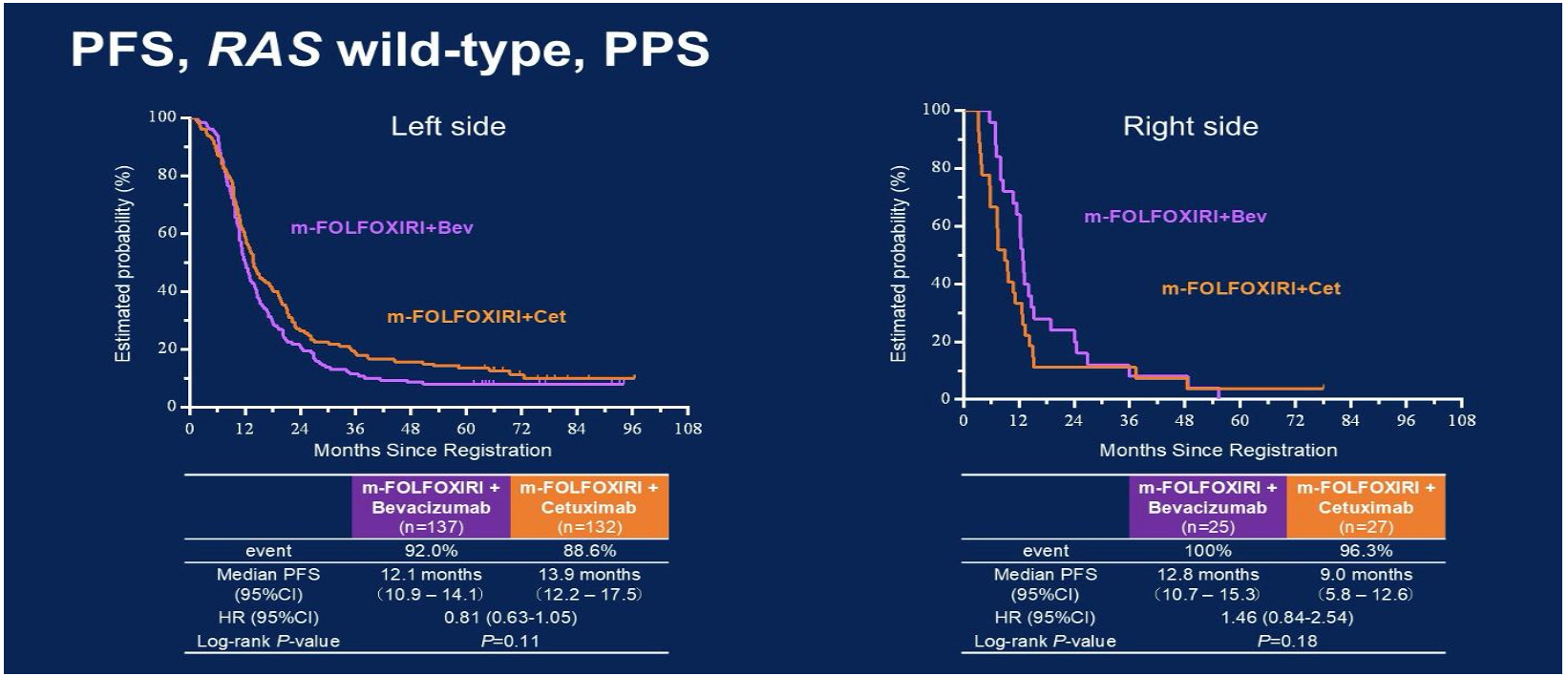
Tratamientos 1L **RAS WT**

DEEPER: Objetivo 2º:SLP



	m-FOLFOXIRI + Bevacizumab (n=137)	m-FOLFOXIRI + Cetuximab (n=132)
event	92.0%	88.6%
Median PFS (95%CI)	12.1 months (10.9 – 14.1)	13.9 months (12.2 – 17.5)
HR (95%CI)	0.81 (0.63-1.05)	
Log-rank *P*-value	*P*=0.11	

	m-FOLFOXIRI + Bevacizumab (n=25)	m-FOLFOXIRI + Cetuximab (n=27)
event	100%	96.3%
Median PFS (95%CI)	12.8 months (10.7 – 15.3)	9.0 months (5.8 – 12.6)
HR (95%CI)	1.46 (0.84-2.54)	
Log-rank *P*-value	*P*=0.18	

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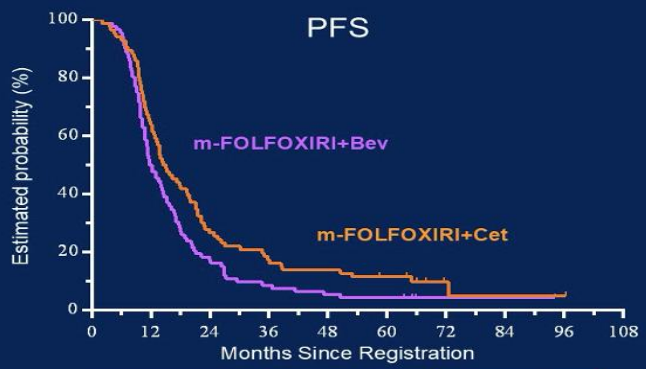
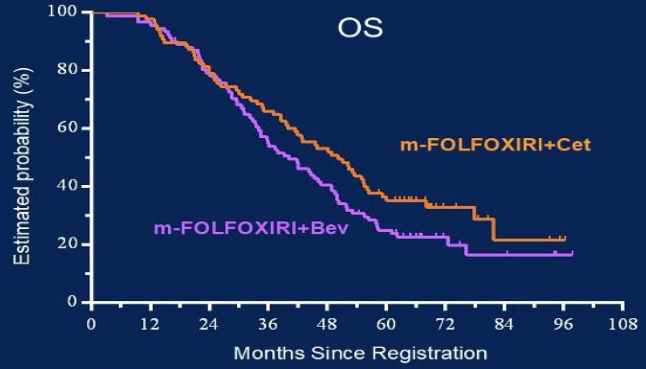
Tratamientos 1L **RAS WT**

DEEPER: SLP y SG en colon izquierdo cuando seleccionamos RAS/BRAF WT

PFS and OS, *RAS*/*BRAF* wild-type and left-sided, PPS



	m-FOLFOXIRI + Bevacizumab (n=92)	m-FOLFOXIRI + Cetuximab (n=86)
event	95.7%	90.7%
Median PFS (95%CI)	11.9 months (10.8 – 14.6)	14.8 months (12.6 – 19.4)
HR (95%CI)	0.71 (0.52-0.97)	
Log-rank *P*-value	*P*=0.029	

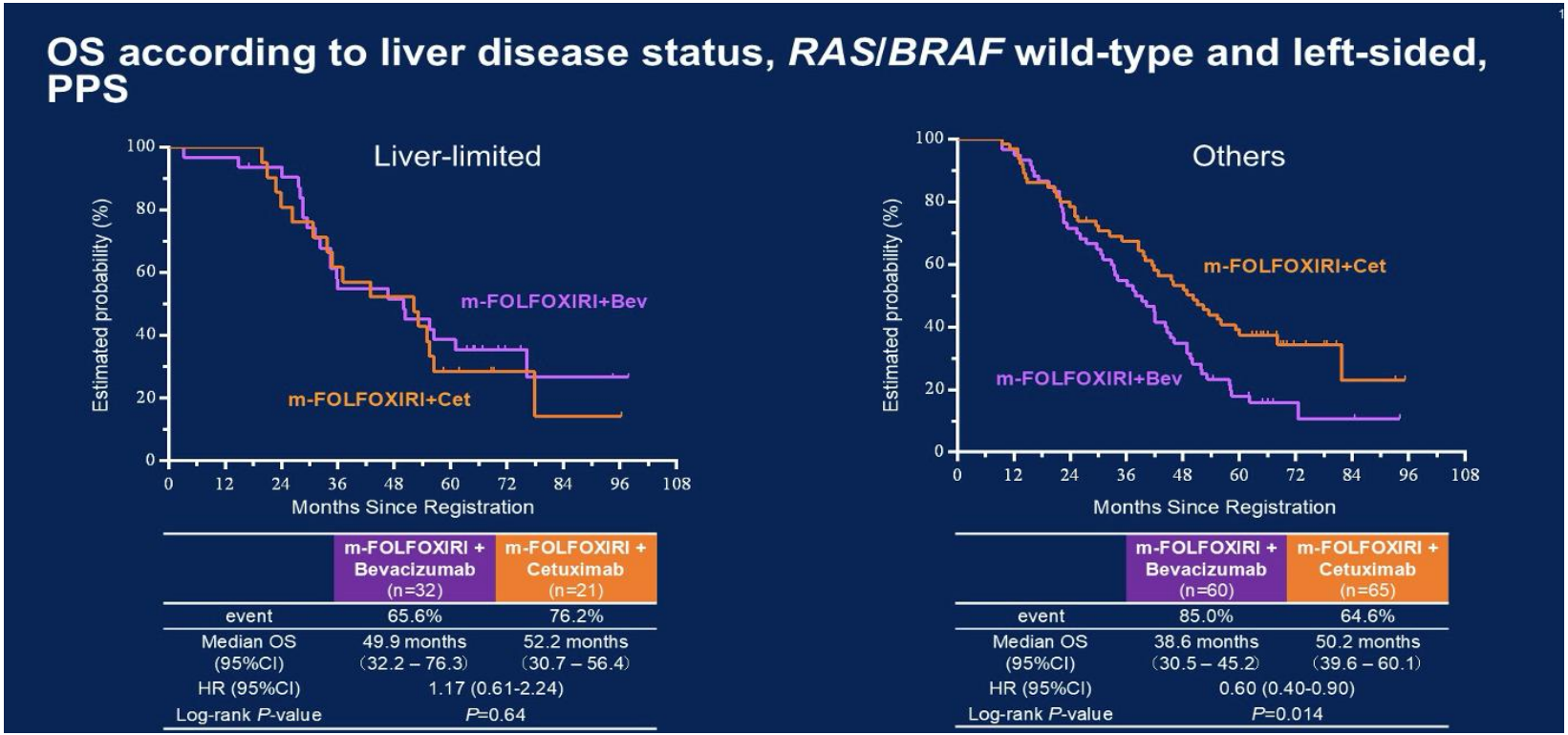


	m-FOLFOXIRI + Bevacizumab (n=92)	m-FOLFOXIRI + Cetuximab (n=86)
event	78.3%	67.4%
Median OS (95%CI)	40.2 months (33.5 – 48.8)	50.2 months (39.9 – 56.0)
HR (95%CI)	0.74 (0.53-1.05)	
Log-rank *P*-value	*P*=0.091	

Tsuji et al. ASCOGI2025.Abtract17

Tratamientos 1L **RAS WT**

DEEPER: SG colon izquierdo según localización de metástasis



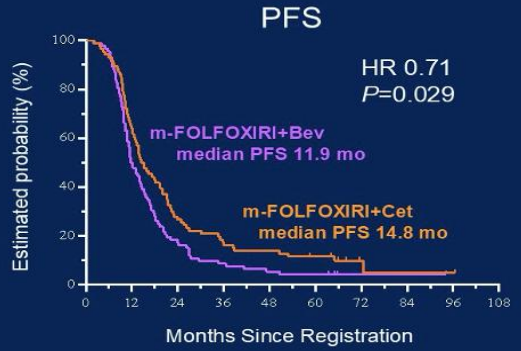
	m-FOLFOXIRI + Bevacizumab (n=32)	m-FOLFOXIRI + Cetuximab (n=21)
event	65.6%	76.2%
Median OS (95%CI)	49.9 months (32.2 – 76.3)	52.2 months (30.7 – 56.4)
HR (95%CI)	1.17 (0.61-2.24)	
Log-rank *P*-value	*P*=0.64	

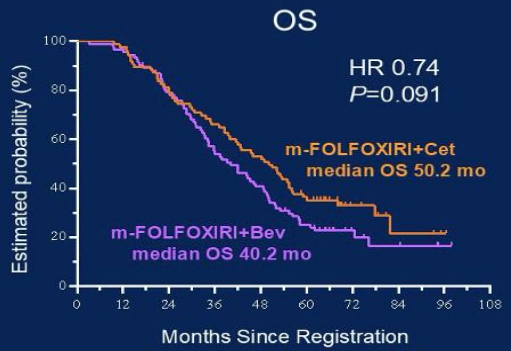
	m-FOLFOXIRI + Bevacizumab (n=60)	m-FOLFOXIRI + Cetuximab (n=65)
event	85.0%	64.6%
Median OS (95%CI)	38.6 months (30.5 – 45.2)	50.2 months (39.6 – 60.1)
HR (95%CI)	0.60 (0.40-0.90)	
Log-rank *P*-value	*P*=0.014	

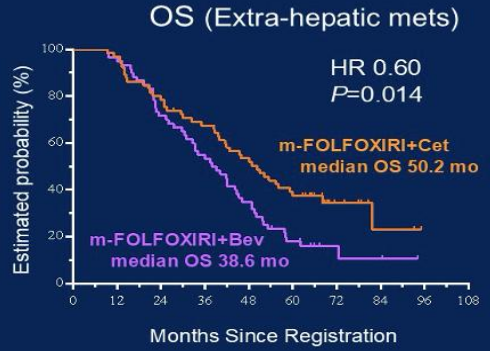
Tsuji et al. ASCOGI2025.Abtract17

Tratamientos 1L **RAS WT**
Mensajes

Key Takeaway Points/Conclusions





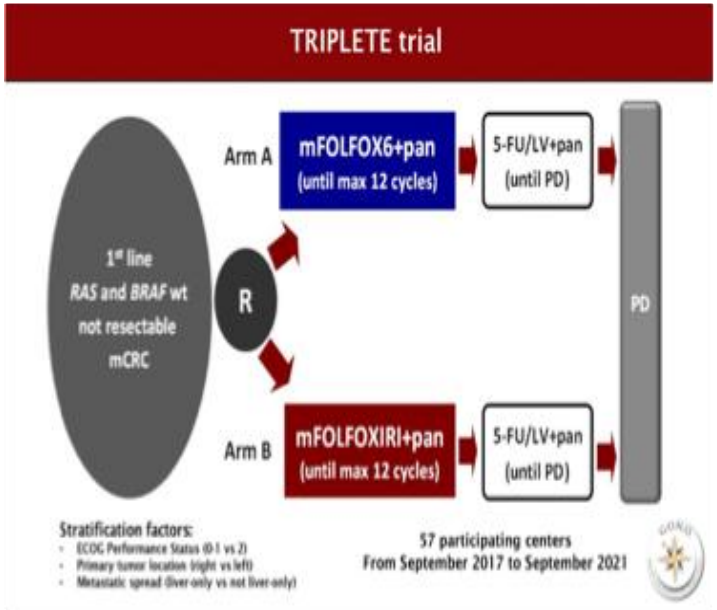


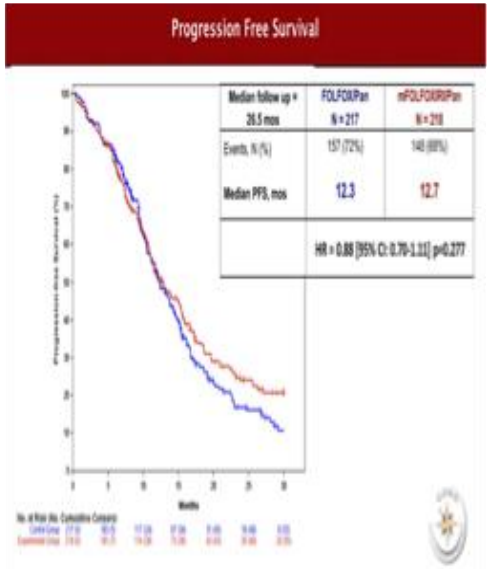
- The DEEPER trial demonstrated **favorable PFS and OS** with modified-FOLFOXIRI plus cetuximab in patients with *RAS*/*BRAF* wild-type and left-sided mCRC.
- The modified-FOLFOXIRI plus cetuximab regimen may be a good option for initial therapy, offering longer survival times in patients **with extra-hepatic metastases**.

Tsuji et al. ASCOGI2025.Abtract17

CONTEXTUALIZACIÓN

¿Me va a cambiar el estudio DEEPER mi práctica clínica?



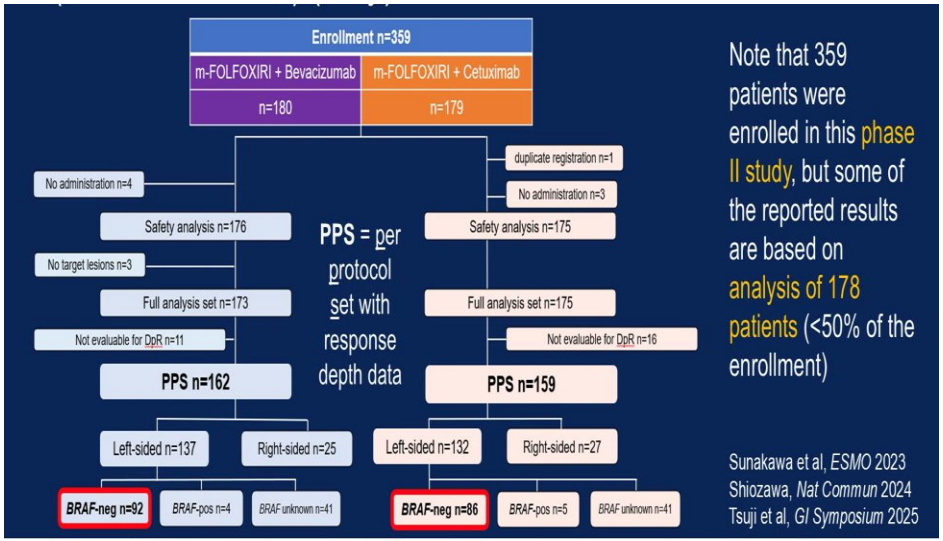


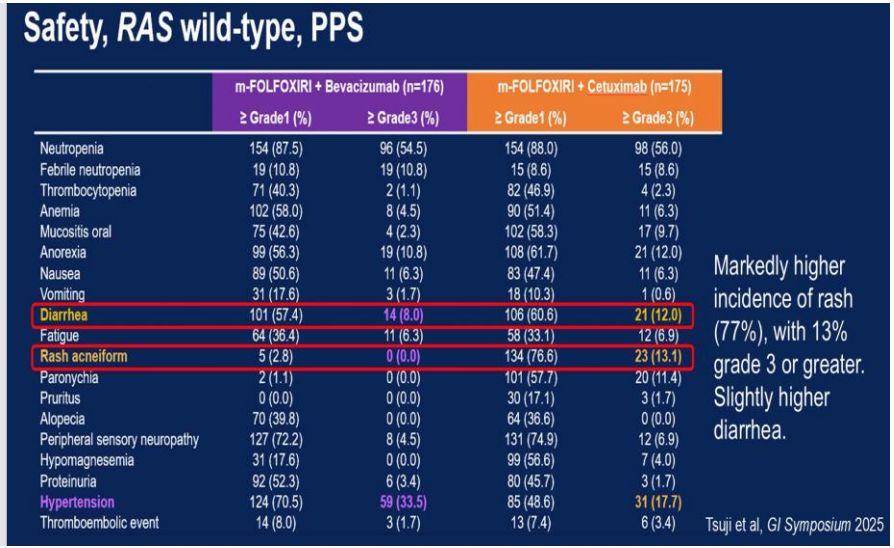
	FOLFOXIRIPan N = 213	mFOLFOXIRIPan N = 218	OR [95%CI], p
Complete Response	7%	7%	
Partial Response	69%	66%	
Response Rate	76%	73%	0.87 [0.56-1.34], p=0.526
Stable disease	17%	18%	
Progressive Disease	5%	5%	
Not Assessed	2%	4%	
R0 Resection Rate	29%	25%	0.81 [0.53-1.23], p=0.317

Rossini D,. J Clin Oncol. 2022 Sep 1;40(25):2878-2888.

CONTEXTUALIZACIÓN

¿Me va a cambiar el estudio DEEPER mi práctica clínica?





	m-FOLFOXIRI + Bevacizumab (n=176)		m-FOLFOXIRI + Cetuximab (n=175)	
	≥ Grade1 (%)	≥ Grade3 (%)	≥ Grade1 (%)	≥ Grade3 (%)
Neutropenia	154 (87.5)	96 (54.5)	154 (88.0)	98 (56.0)
Febrile neutropenia	19 (10.8)	19 (10.8)	15 (8.6)	15 (8.6)
Thrombocytopenia	71 (40.3)	2 (1.1)	82 (46.9)	4 (2.3)
Anemia	102 (58.0)	8 (4.5)	90 (51.4)	11 (6.3)
Mucositis oral	75 (42.6)	4 (2.3)	102 (58.3)	17 (9.7)
Anorexia	99 (56.3)	19 (10.8)	108 (61.7)	21 (12.0)
Nausea	89 (50.6)	11 (6.3)	83 (47.4)	11 (6.3)
Vomiting	31 (17.6)	3 (1.7)	18 (10.3)	1 (0.6)
Diarrhea	101 (57.4)	14 (8.0)	106 (60.6)	21 (12.0)
Fatigue	64 (36.4)	11 (6.3)	58 (33.1)	12 (6.9)
Rash acneiform	5 (2.8)	0 (0.0)	134 (76.6)	23 (13.1)
Paronychia	2 (1.1)	0 (0.0)	101 (57.7)	20 (11.4)
Pruritus	0 (0.0)	0 (0.0)	30 (17.1)	3 (1.7)
Alopecia	70 (39.8)	0 (0.0)	64 (36.6)	0 (0.0)
Peripheral sensory neuropathy	127 (72.2)	8 (4.5)	131 (74.9)	12 (6.9)
Hypomagnesemia	31 (17.6)	0 (0.0)	99 (56.6)	7 (4.0)
Proteinuria	92 (52.3)	6 (3.4)	80 (45.7)	3 (1.7)
Hypertension	124 (70.5)	59 (33.5)	85 (48.6)	31 (17.7)
Thromboembolic event	14 (8.0)	3 (1.7)	13 (7.4)	6 (3.4)

Rossini D,. J Clin Oncol. 2022 Sep 1;40(25):2878-2888.

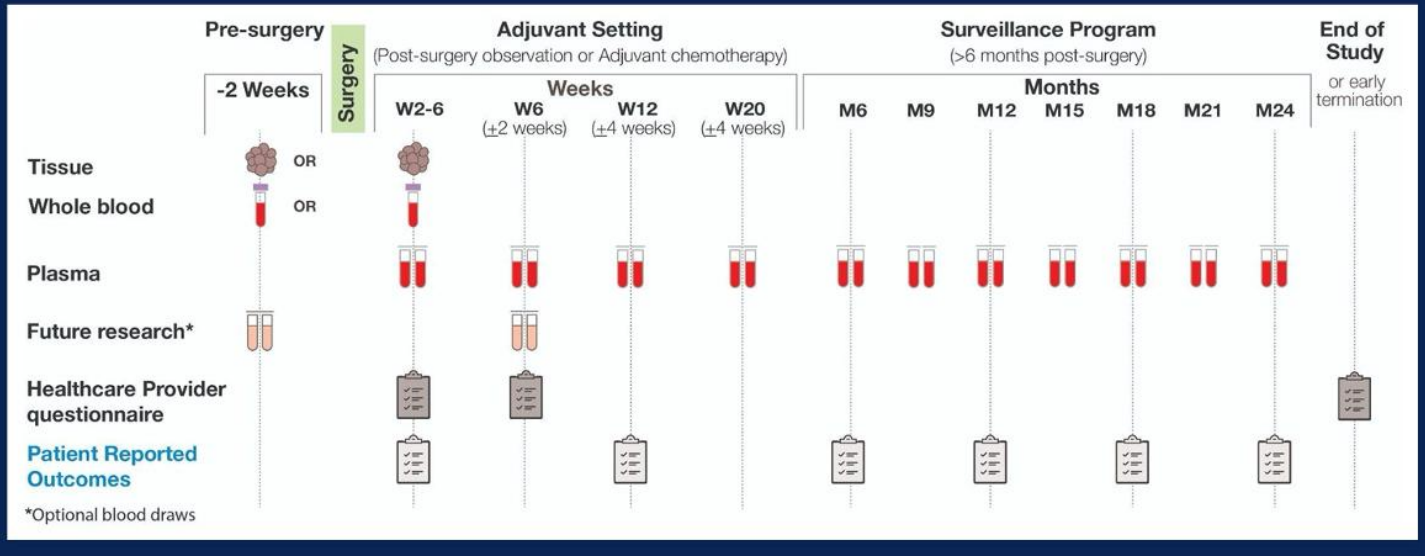
BLOQUE II

BIOPSIA LÍQUIDA EN ENFERMEDAD LOCALIZADA

Biopsia Líquida

Estudio BESPOKE : Diseño

BESPOKE CRC (NCT04264702) is a multicenter (133 US sites), prospective, observational study evaluating the ability of a tumor-informed, personalized ctDNA assay (Signatera™, Natera, Inc.) to inform ACT treatment decisions in patients with pathologic stage II/III CRC.[1]



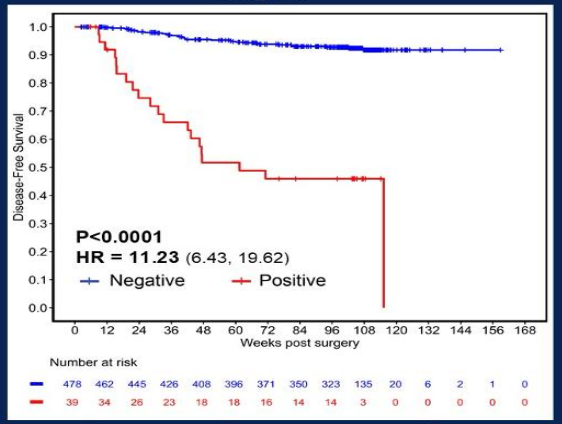
Shah. ASCOGI2025.Abstract15

Biopsia Líquida

Estudio BESPOKE : Diseño

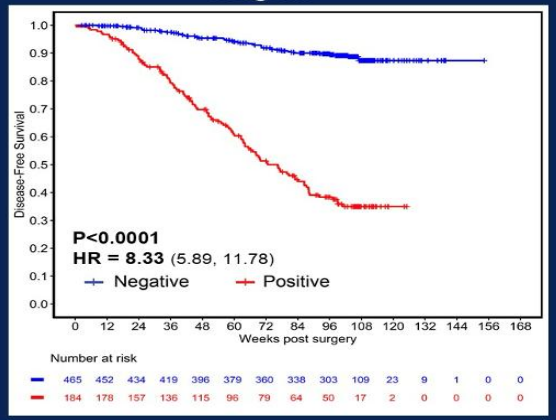
Post-operative ctDNA positivity predicts inferior DFS

Stage II



ctDNA Status	Events	Median DFS post surgery, months (95%)	2-year DFS post surgery,% (95% CI)
Negative	33	NE (NE-NE)	**91.8** (NE-NE)
Positive	20	12.7 (8.3-NE)	**45.9** (32.1-65.8)

Stage III



ctDNA Status	# Events	Median DFS post surgery, months (95%)	2-year DFS post surgery,% (95% CI)
Negative	47	NE (NE-NE)	**87.4** (83.8-91.1)
Positive	105	16.2 (13.6-18.9)	**35.5** (28.6-44.2)

Landmark DFS Analysis at 6 weeks (42 Days). NE: Not Estimable

Shah. ASCOGI2025.Abstract15

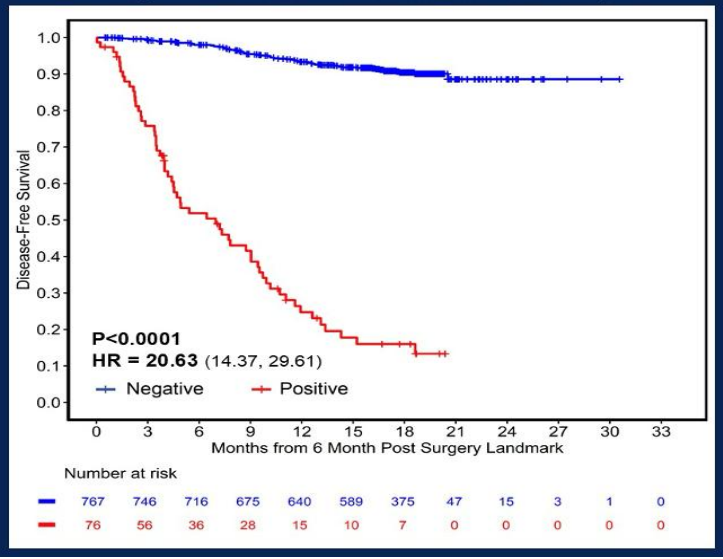
Biopsia Líquida

Estudio BESPOKE : Resultados

First surveillance Signatera timepoint positivity predicts inferior DFS

8

DFS by ctDNA status - 1st surveillance timepoint



Time-dependent of DFS during Surveillance stratified by Signatera Status

Stage	Hazard Ratio	Confidence Interval	p-value
Stage II/III	**26.4**	21.6 - 32.4	**<0.0001**

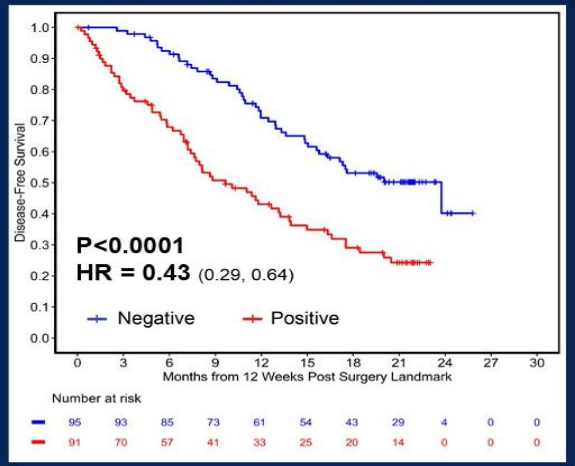
Shah. ASCOGI2025.Abstract15

Biopsia Líquida

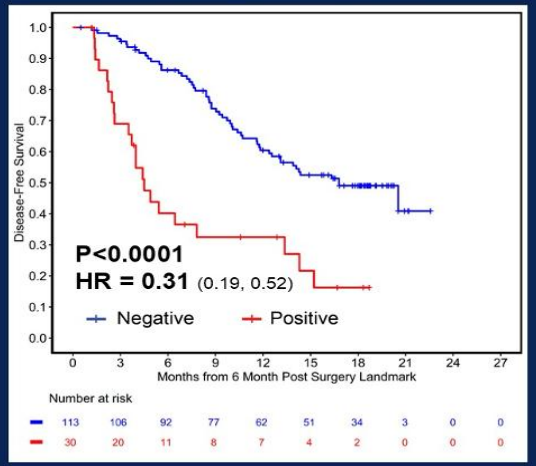
Estudio BESPOKE : Resultados

ctDNA clearance during and after ACT is associated with superior DFS

ctDNA clearance by Month 3



ctDNA clearance by Month 6



ctDNA clearance in MRD-pos (N=180)		
Clearance time point	Number who cleared	Clearance rate % (95% CI)
Week 12	89	**49.44** (42.2-56.7)
Week 20	121	**67.22** (60.1-73.7)
Month 6	132	**73.33** (66.4-79.3)
Overall	136	**75.56** (68.8-81.3)

Shah. ASCOGI2025.Abstract15

Biopsia Líquida

Estudio BESPOKE : Conclusiones

1.El mayor estudio de BL de USA :la BL cambia el manejo de la adyuvancia **en 1 de cada 6 pacientes.**

2. El ctDNA demuestra alta **sensibilidad** en detectar recidivas :hasta en pulmón y peritoneo.

3.La **positividad se correlaciona con MRD , menos SLR .**

4.La adyuvancia solo beneficia a positivos.

5.Aclarar a los 3 y 6 meses más SLR.

6.En + estrategias que permiten manejar como oligomx.

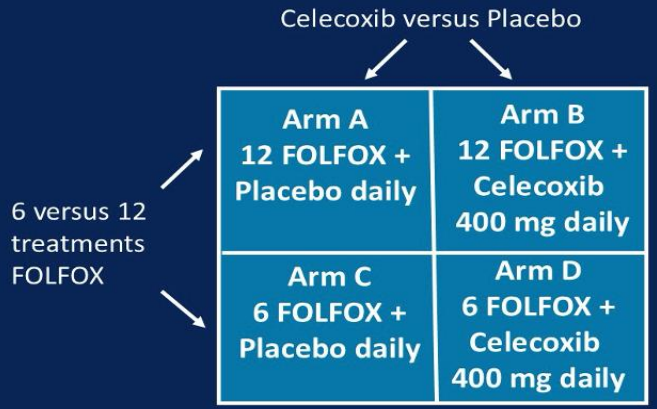
Shah. ASCOGI2025.Abstract15

Biopsia Líquida

Estudio CALGB :Diseño (3 años de celecoxib)

CALGB/SWOG 80702 trial

- **Estadio III**
- **Obj.1º:SLR**



Celecoxib/placebo continued for a total of 3 years from the day that study drug was initiated.

Target sample size = 2,500
Actual final accrual = 2,526

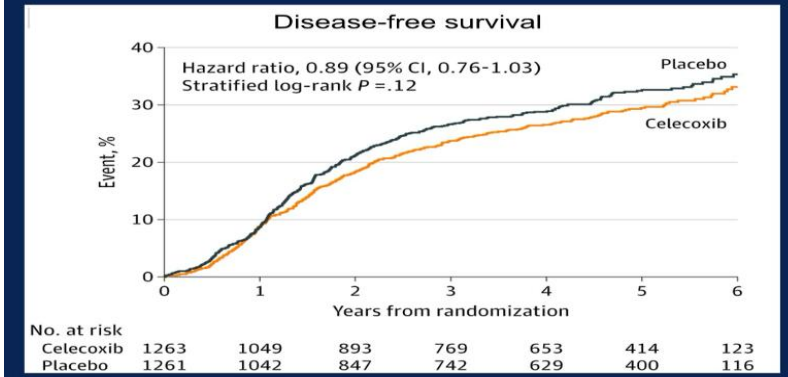
Nowak.ASCOGI2025.Abstract LBA14

Biopsia Líquida

Estudio CALGB :SG

SLR con celecoxib (negativa)

Survival according to adjuvant celecoxib use in 80702



- No statistically significant association between celecoxib treatment and DFS
- Effect of celecoxib treatment did not significantly differ according to assigned adjuvant FOLFOX duration
- However, the HR of 0.89 and the Kaplan-Meier curve separation implied a potential benefit in subgroups of participants

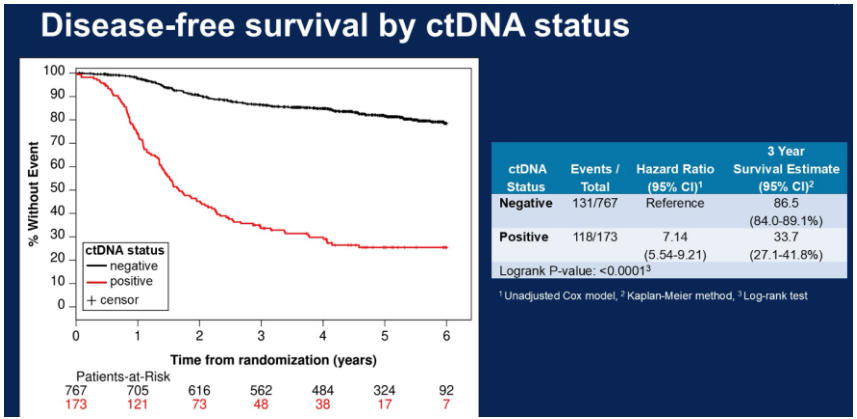
Meyerhardt JA, et al. JAMA 325(13):1277-1286. 2021.

Meyerhardt JA, JAMA. 2021 Apr 6;325(13):1277-1286.

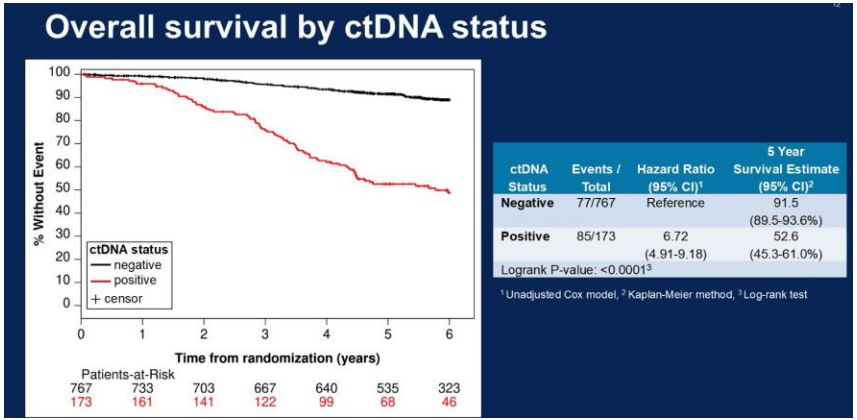
Biopsia Líquida

Estudio CALGB : Papel pronóstico de ctDNA

Menos SLR



Menos SG

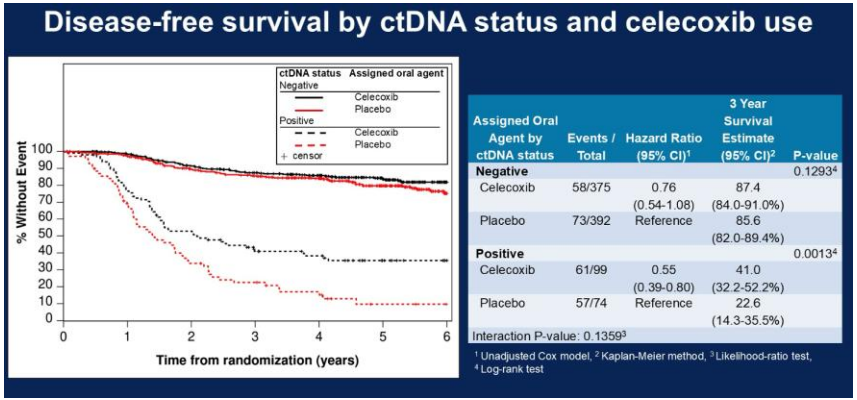


Nowak.ASCOGI2025.Abstract LBA14

Biopsia Líquida

Estudio CALGB :Interacción de ctDNA y uso de celecoxib

Beneficio SLE si BL+ y uso celecoxib

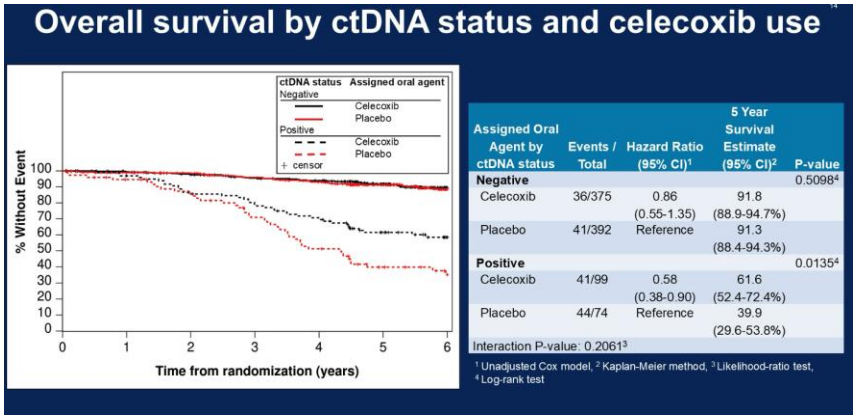


Assigned Oral Agent by ctDNA status	Events / Total	Hazard Ratio (95% CI)[1]	3 Year Survival Estimate (95% CI)[2]	P-value
Negative				0.1293[4]
Celecoxib	58/375	0.76 (0.54-1.08)	87.4 (84.0-91.0%)	
Placebo	73/392	Reference	85.6 (82.0-89.4%)	
Positive				0.0013[4]
Celecoxib	61/99	0.55 (0.39-0.80)	41.0 (32.2-52.2%)	
Placebo	57/74	Reference	22.6 (14.3-35.5%)	

Interaction P-value: 0.1359[3]

[1] Unadjusted Cox model, [2] Kaplan-Meier method, [3] Likelihood-ratio test, [4] Log-rank test

Beneficio en SG



Assigned Oral Agent by ctDNA status	Events / Total	Hazard Ratio (95% CI)[1]	5 Year Survival Estimate (95% CI)[2]	P-value
Negative				0.5098[4]
Celecoxib	36/375	0.86 (0.55-1.35)	91.8 (88.9-94.7%)	
Placebo	41/392	Reference	91.3 (88.4-94.3%)	
Positive				0.0135[4]
Celecoxib	41/99	0.58 (0.38-0.90)	61.6 (52.4-72.4%)	
Placebo	44/74	Reference	39.9 (29.6-53.8%)	

Interaction P-value: 0.2061[3]

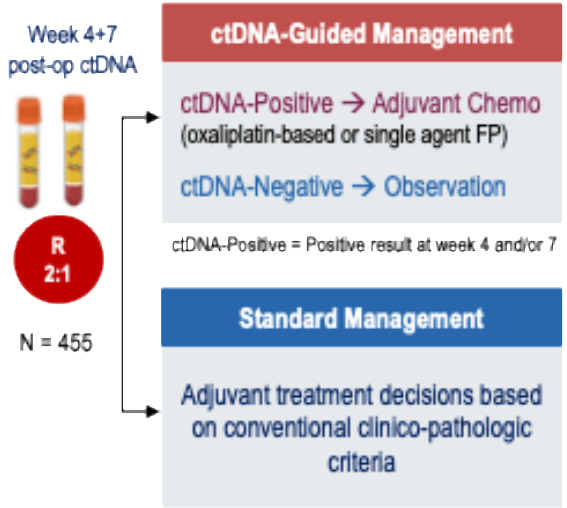
[1] Unadjusted Cox model, [2] Kaplan-Meier method, [3] Likelihood-ratio test, [4] Log-rank test

"La positividad define un subgrupo que se benefician del uso de celecoxib adyuvante"

Nowak.ASCOGI2025.Abstract LBA14

Biopsia Líquida
CONTEXTUALIZACIÓN

DYNAMIC – phase 2 multicenter randomized in stage II colon cancer



Tie et al, N Engl J Med 2022

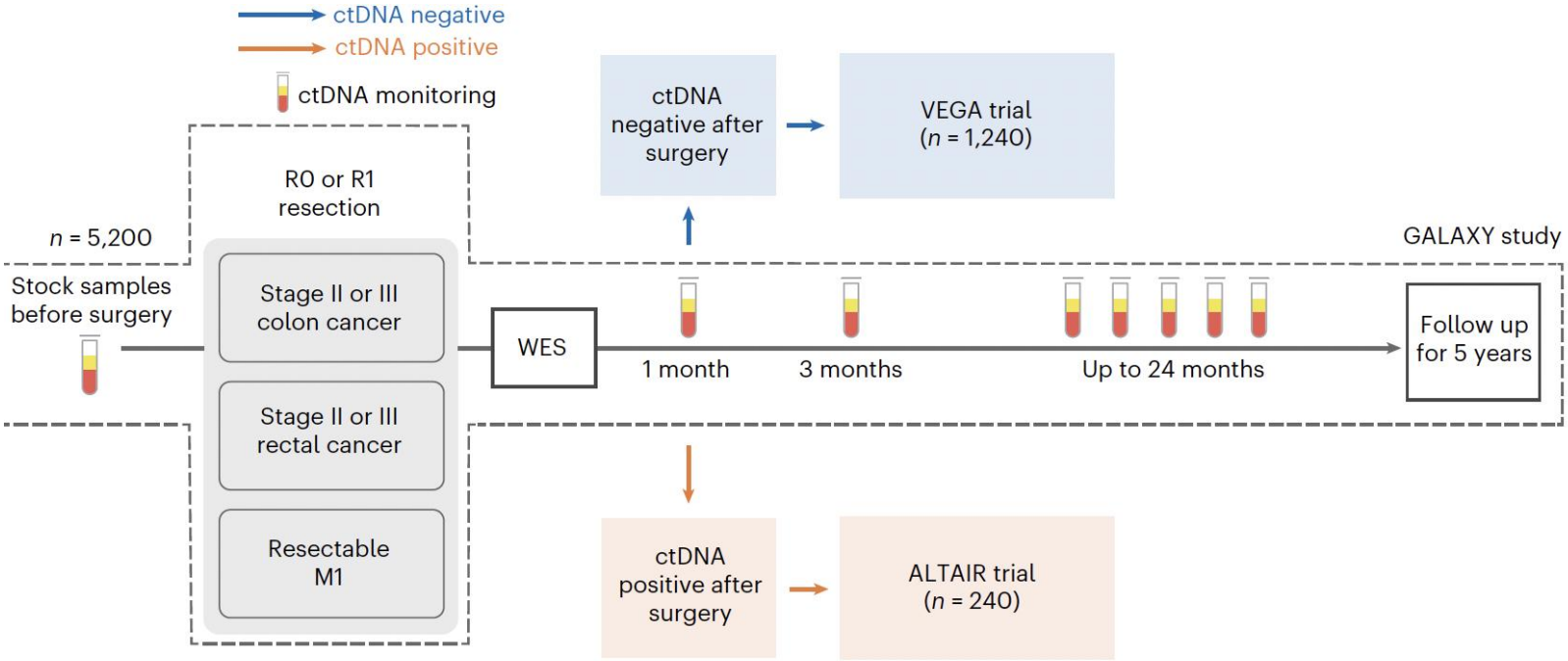
ctDNA-guided approach:

- **Was not inferior** to SOC (2Y RFS 93% vs 92%)
- **Significantly reduced by half the proportion of patients receiving adjuvant chemotherapy** (28% vs 15%)

Biopsia Líquida

CONTEXTUALIZACIÓN GALAXY study (Circulate Japan ,sgmto 23 ms)

Observacional, n:2240

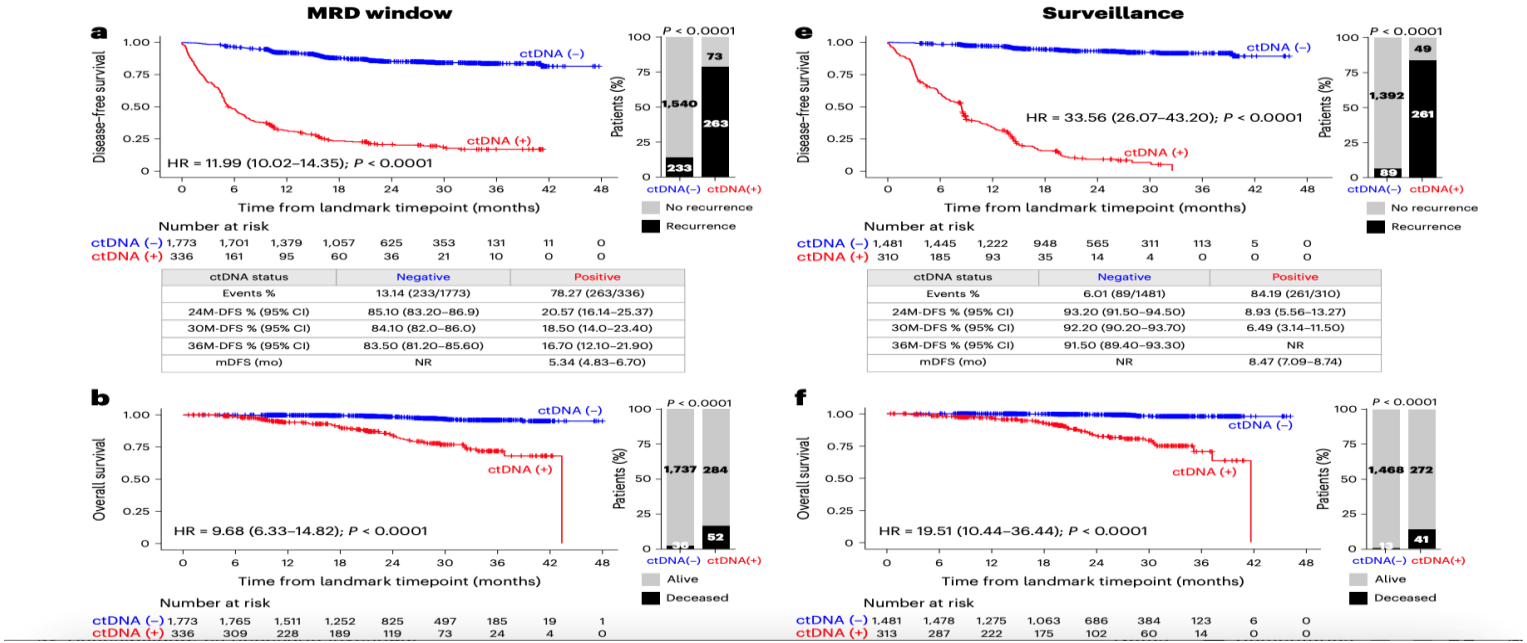


Nakamura Y, Nat Med. 2024 Nov;30(11):3272-3283.

Biopsia Líquida

CONTEXTUALIZACIÓN GALAXY study (Circulate Japan ,sgmto 23 ms)

Observacional, n:2240



Nakamura Y, Nat Med. 2024 Nov;30(11):3272-3283.

Biopsia Líquida

CONTEXTUALIZACIÓN GALAXY study (Circulate Japan ,sgmto 23 ms)

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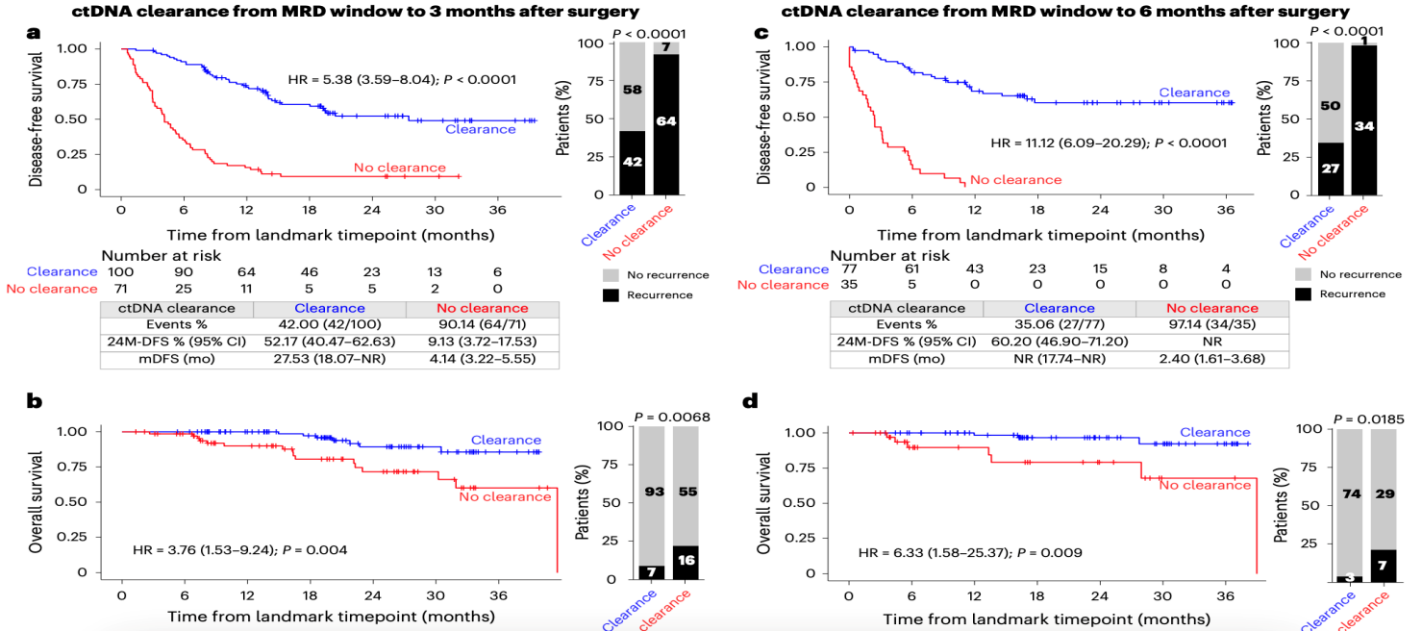


ctDNA clearance	Clearance	No clearance
Events %	42.00 (42/100)	90.14 (64/71)
24M-DFS % (95% CI)	52.17 (40.47–62.63)	9.13 (3.72–17.53)
mDFS (mo)	27.53 (18.07–NR)	4.14 (3.22–5.55)

ctDNA clearance	Clearance	No clearance
Events %	35.06 (27/77)	97.14 (34/35)
24M-DFS % (95% CI)	60.20 (46.90–71.20)	NR
mDFS (mo)	NR (17.74–NR)	2.40 (1.61–3.68)

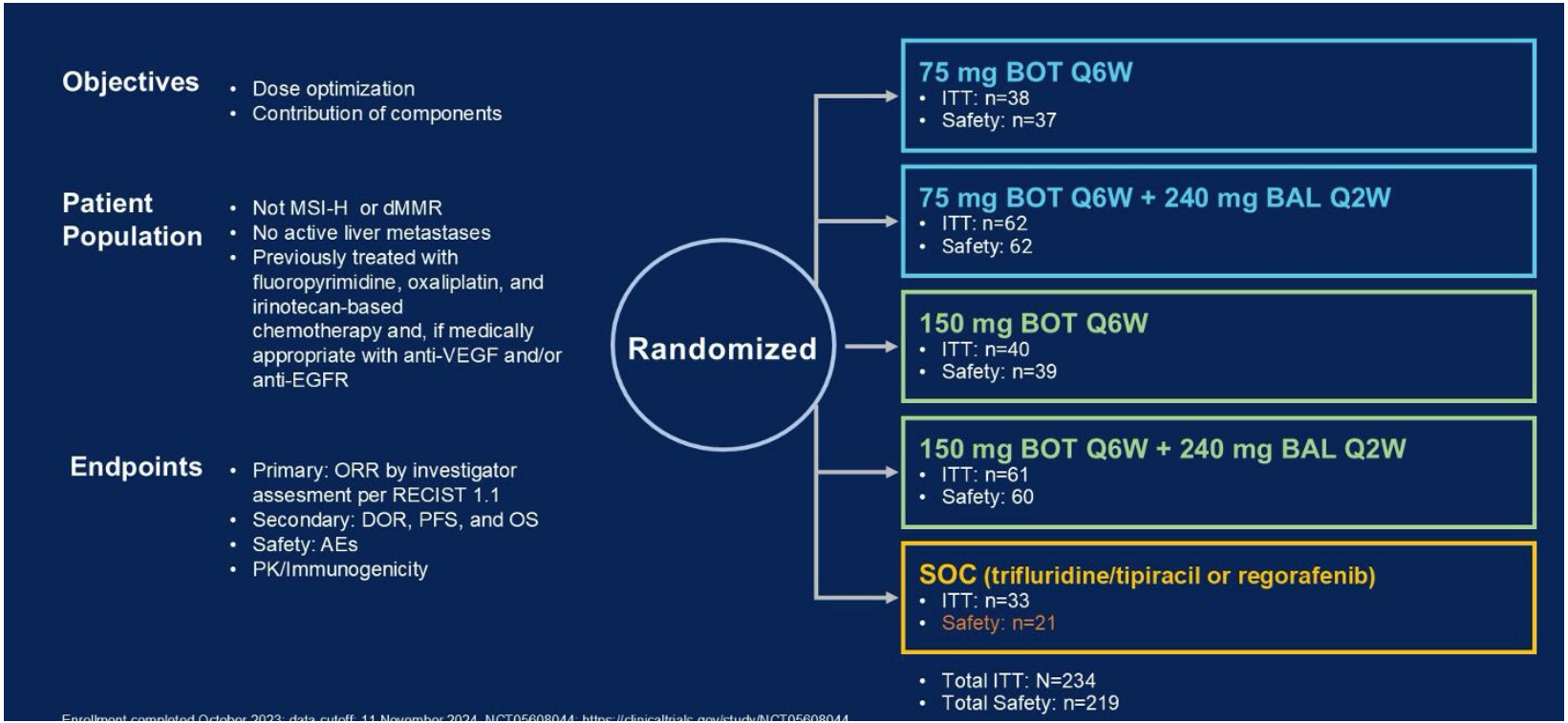
Nakamura Y, Nat Med. 2024 Nov;30(11):3272-3283.

BLOQUE III

COLON REFRACTARIO

Colon Refractario

BOT/BAL: Diseño Fase II



Fakik.ASCOGI2025.Abstract23

Colon Refractario

BOT/BAL: Resultados

	BOT 75 mg Q6W		BOT 150 mg Q6W		SOC
	BOT / BAL n=62	Monotherapy n=38	BOT / BAL n=61	Monotherapy n=40	Trifluridine/Tipiracil or Regorafenib n=33
Confirmed ORR, n (%)	12 (19%)	0 (0%)	5 (8%)	3 (8%)	0 (0%)
95% CI	10–31	0–9	3–18	2–20	0–9
CR	0 (0)	0 (0)	0 (0)	1 (3)	0 (0)
PR	12 (19)	0 (0)	5 (8)	2 (5)	0 (0)
SD	22 (35)	14 (37)	28 (46)	12 (30)	12 (36)
PD	26 (42)	20 (53)	23 (38)	21 (53)	8 (24)
NE	2 (3)	4 (11)	5 (8)	4 (10)	13 (39)
DCR, n (%)	34 (55)	14 (37)	33 (54)	15 (38)	12 (36)
95% CI	42–68	22–54	41–67	23–54	20–55
Median follow up, months (range)	12.7 (1.6–19.7)	9.8 (0.6–17.7)	12.9 (0.1–20.6)	13.4 (0.7–21.1)	10.9 (0.0–17.7)

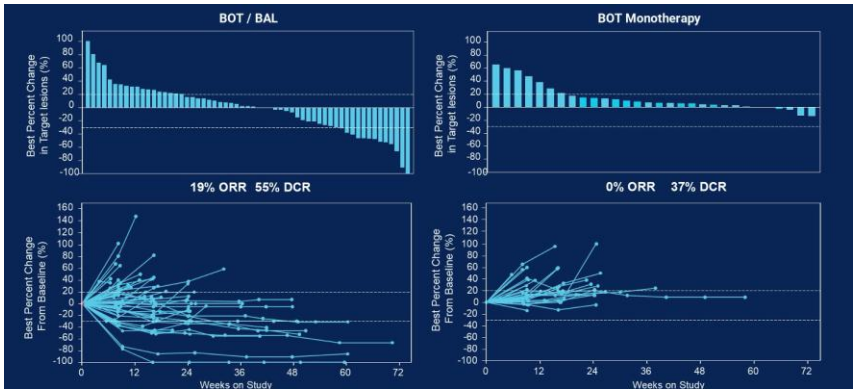
DOR not mature with **14/20 (70%)** of responses ongoing

Fakik.ASCOGI2025.Abstract23

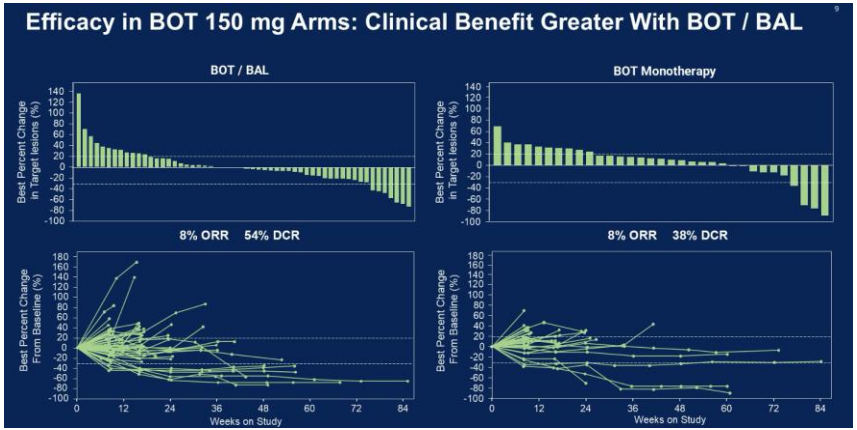
Colon Refractario

BOT/BAL: ¿Qué dosis?

TR BOT 75



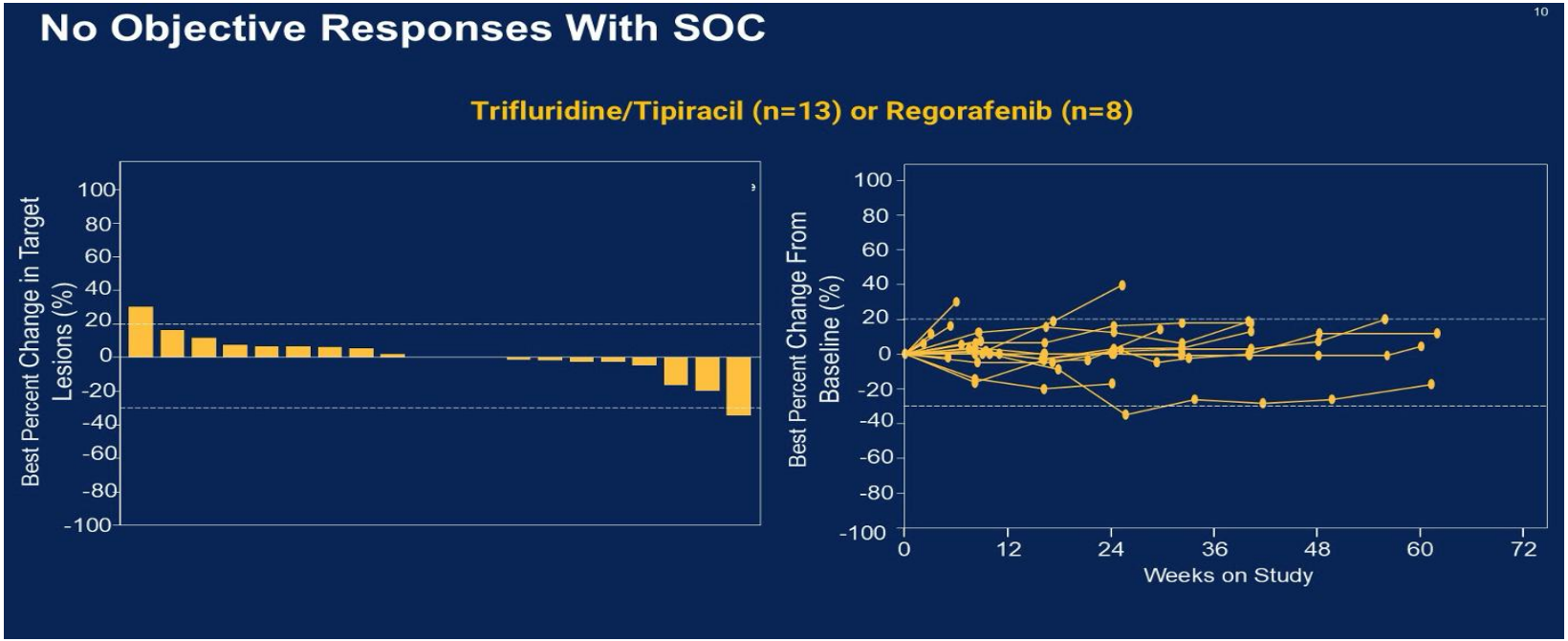
TR BOT 150



Fakik.ASCOGI2025.Abstract23

Colon Refractario

BOT/BAL: Sin respuestas en SoC



Fakik.ASCOGI2025.Abstract23

Colon Refractario

BOT/BAL: Toxicidad

	BOT 75 mg Q6W		BOT 150 mg Q6W		SOC
	BOT / BAL n=62	BOT Mono n=37	BOT / BAL n=60	BOT Mono n=39	Trifluridine/Tipiracil or Regorafenib n=21
Any TRAE, n (%)	54 (87)	28 (76)	60 (100)	31 (79)	19 (90)
Grade ≥3	22 (35)	8 (22)	26 (43)	9 (23)	12 (57)
Any imAE, n (%)	38 (61)	20 (54)	49 (82)	18 (46)	1 (5)
Diarrhea/colitis[a]	22 (35)	14 (38)	30 (50)	13 (33)	0 (0)
Hypothyroidism[a]	8 (13)	0 (0)	15 (25)	0 (0)	0 (0)
Skin[a]	4 (6)	2 (8)	17 (28)	1 (3)	0 (0)
Grade ≥3	20 (32)	7 (19)	24 (40)	10 (26)	1 (5)
Diarrhea/colitis[b]	11 (18)	4 (11)	16 (27)	7 (18)	0 (0)
Pneumonitis[b]	2 (3)	1 (3)	2 (3)	0 (0)	1 (5)
Hepatitis[b]	1 (2)	2 (5)	1 (2)	2 (5)	0 (0)

[a]Top-most common imAE. [b]Grade ≥3 imAE in ≥5% of patients.

- 75 mg BOT / BAL best risk-benefit and selected for phase 3
- No treatment-related deaths
- No new safety signals

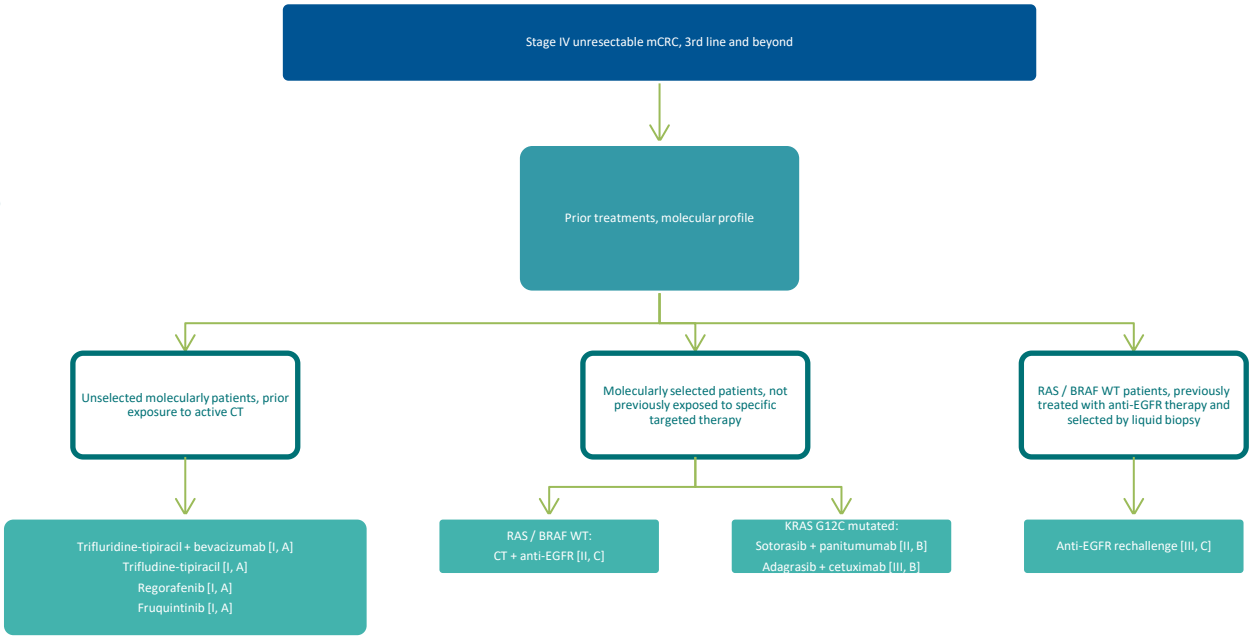
Fakik.ASCOGI2025.Abstract23

Colon Refractario
BOT/BAL: Conclusiones

- Tenemos dosis
- TR elevada comparada con SoC
- Futuro: datos de DOR,SLP, SG

Colon Refractario
CONTEXTUALIZACIÓN

No Liver Metastases
BOT/BAL?



SEOM Living Guidelines 2025

BLOQUE IV

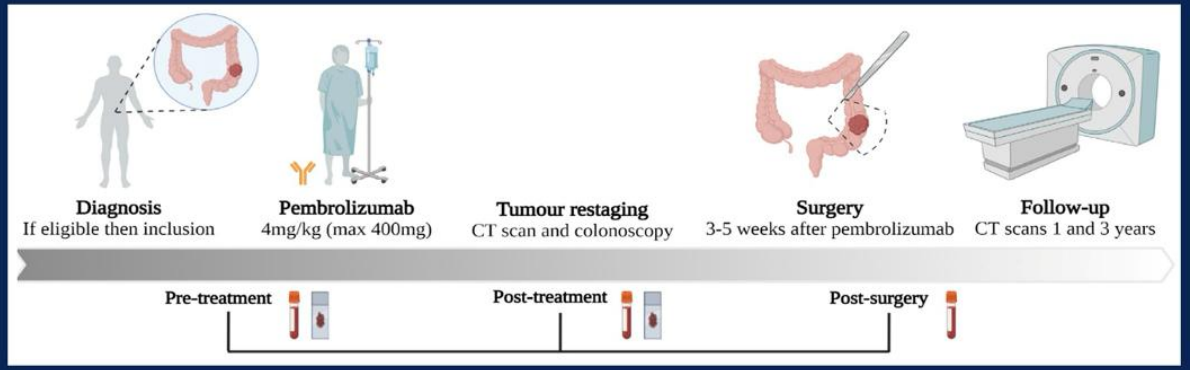
CANCER COLORRECTAL LOCALIZADO

Cáncer de colon localizado MSI-H/dMMR

RESET-C: Diseño

- An investigator-initiated, phase II study of patients with localized dMMR colon cancer[1]

Main inclusioncriterias:
- dMMR stage I-III CC
- No contra-indication for immunotherapy

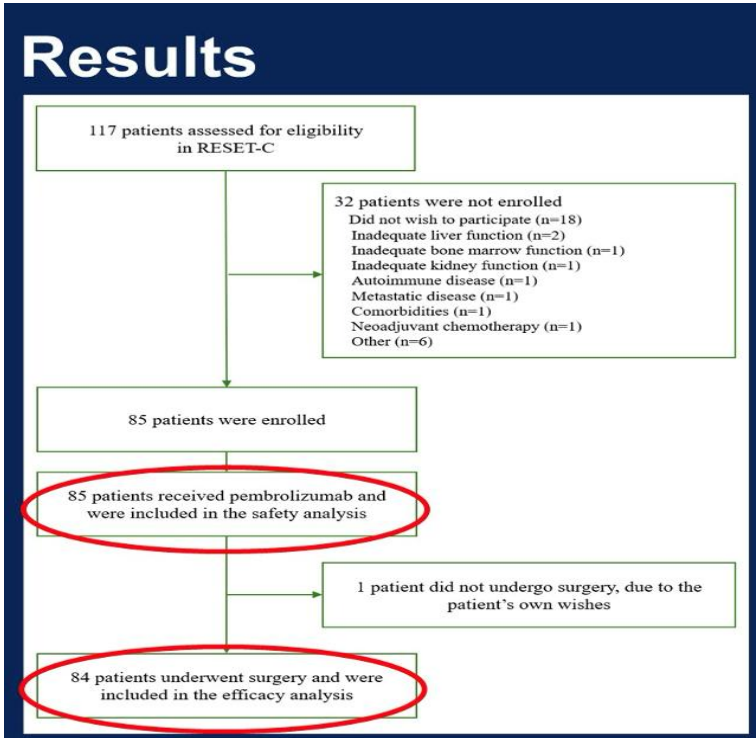


- Primary outcome: pCR rate
- Secondary outcomes: safety, surgical complications, major pathological response, overall survival, disease-free survival, and predictive markers (e.g. biopsies, ctDNA) and endoscopic treatment response evaluation

Qvortrup. ASCOGI2025.Abstract19

Cáncer de colon localizado MSI-H/dMMR

RESET-C: Población incluida

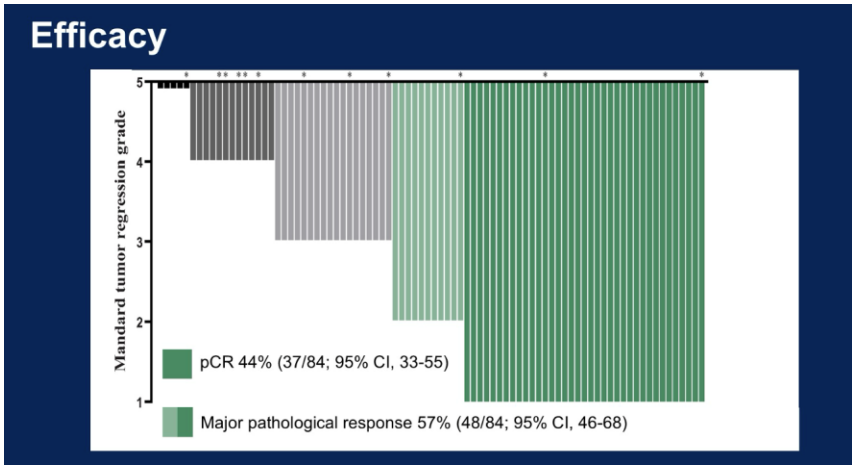


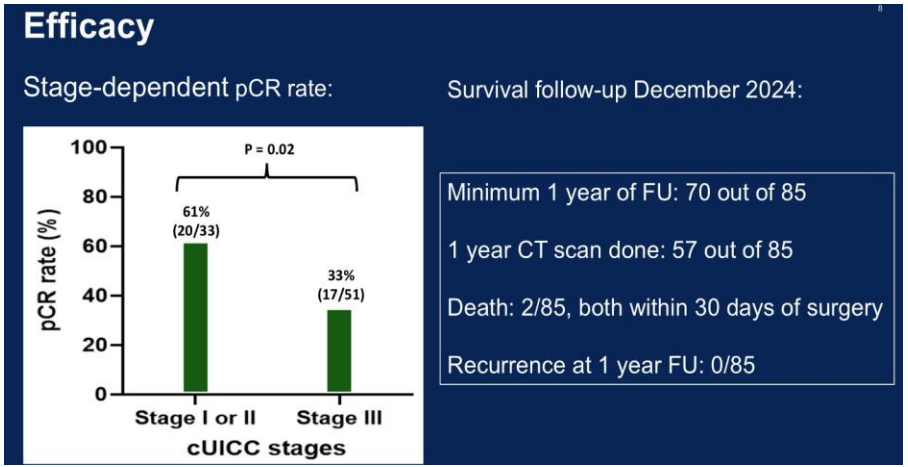
	Patients with localized dMMR tumors (n = 85)
Age at enrollment (years)	
Median (IQR)	74 (68-79)
> 70	55 (65)
Sex	
Female	61 (72%)
Male	24 (28%)
ECOG performance status	
0	52 (61%)
I	33 (39%)
Clinical tumor stage	
T1 or Tx	8 (9%)
T2	21 (25%)
T3	41 (48%)
T4 or T4a	13 (15%)
T4b	2 (2%)
Clinical node stage	
N0	34 (40%)
N1	28 (33%)
N2	23 (27%)
Tumor location	
Right colon	55 (65%)
Transverse colon	19 (22%)
Left colon	11 (13%)

Qvortrup. ASCOGI2025.Abstract19

Cáncer de colon localizado MSI-H/dMMR

RESET-C: Resultados

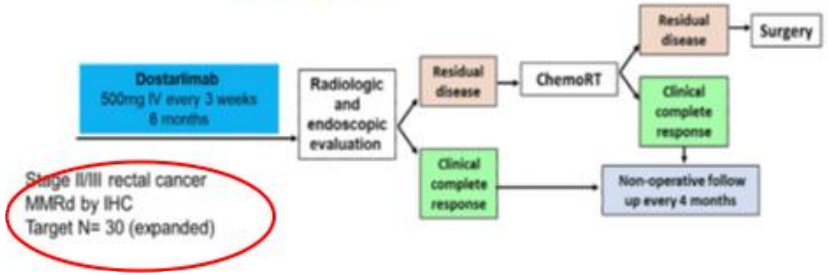




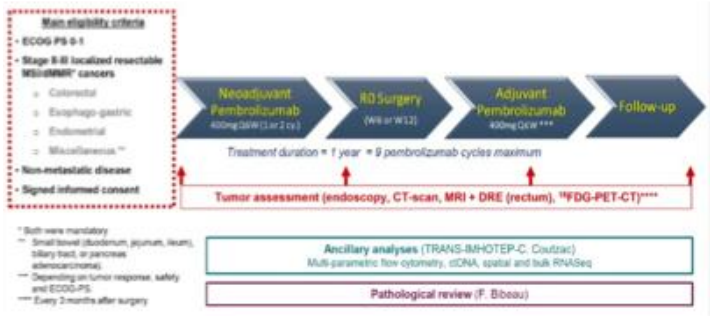
Qvortrup. ASCOGI2025.Abstract19

CONTEXTUALIZACIÓN
Colon Localizado Inestable MSI-H ¿inmuno?

Dorstalimab
(NCT04165772)
(6 meses, **Rectos;**n:48)



Pembrolizumab
(IMHOTEP)
(1 o 2 ciclos, **CCR;**n:77)



- TR general al bloqueo de PD-1 con o sin QT/RDT
- Tasa de respuesta completa patológica (pCR) o respuesta clínica completa (cCR) a los **12 meses** después del bloqueo de PD-1 con o sin QT/RDT

pCR (ypT0N0)

Cercek A, N Engl J Med. 2022 Jun 23;386(25):2363-2376. & Cercek J Clin Oncol 42, 2024 (suppl 17; abstr LBA3512)&C.De la Fouchardiere.Annals of Oncology (2024) 35 (suppl_2): S428-S481.

CONTEXTUALIZACIÓN
Colon Localizado Inestable MSI-H ¿inmuno?

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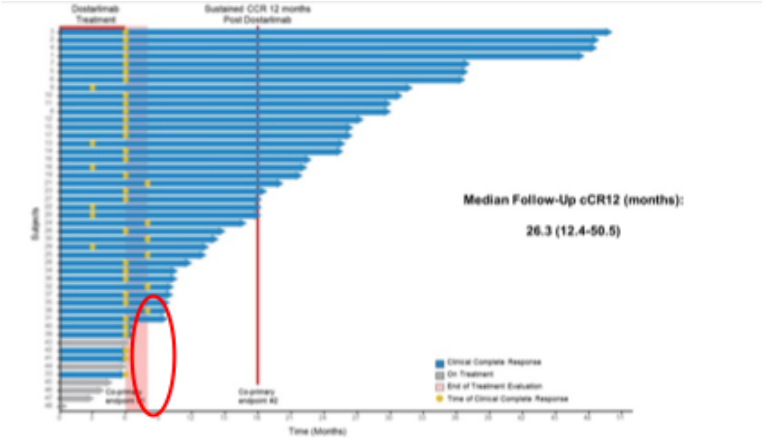


TR (cCR) 100%
Todos a los 12 meses

Pembrolizumab
(IMHOTEP)
(1 o 2 ciclos, CCR;n:77)

ypT0N0: 52,8%

	Colon (N=63)		Rectum (N=9)		All CRC (N=72)	
pCR (ypT0N0) rate	**35/63**	**(55.6%)**	**3/9**	**(33.3%)**	**38/72**	**(52.8%)**
After 1 pembrolizumab cycle	21/45	(46.7%)	2/5	(40.0%)	23/50	(46.0%)
After 2 pembrolizumab cycles	14/18	(77.8%)	1/4	(25.0%)	**15/22**	**(68.2%)**

* Multivariate logistic analysis
p=0.034

Cercek A, N Engl J Med. 2022 Jun 23;386(25):2363-2376. & Cercek J Clin Oncol 42, 2024 (suppl 17; abstr LBA3512)&C.De la Fouchardiere.Annals of Oncology (2024) 35 (suppl_2): S428-S481.

CONTEXTUALIZACIÓN
Colon Localizado Inestable MSI-H ¿inmuno?

NICHE-2
(n:115),dos ciclos

Objetivos Primarios:
Seguridad y SLE a 3 años

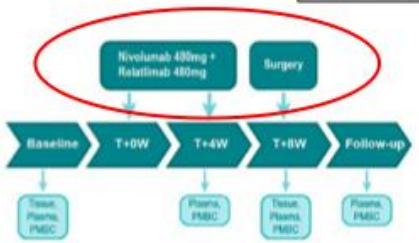
Key eligibility criteria
- Non-metastatic dMMR colon cancer, previously untreated
- cT3 and/or N+ based on radiographic staging
- No clinical or radiologic signs of obstruction or perforation

Pacs de alto riesgo (64% cT4,N+ 67%)

NICHE-3
(n:59) dos ciclos, más dosis de Nivo

Objetivo Primario:
pRC (≤50% células viables tumorales)

Main inclusion criteria
- Non-metastatic dMMR colon cancer, previously untreated
- cT3 and/or N+ based on radiographic staging
- No clinical or radiographic signs of obstruction or perforation
- No active auto-immune disease or use of systemic steroids/immunosuppressive medications



Pacs de alto riesgo (68% cT4,N+ 63%)

Chalabi M, C N Engl J Med. 2024 Jun 6;390(21):1949-1958. &Chalabi. Annals of Oncology (2024) 35 (suppl_2): 1-72.&P.G.M. de Gooyer of Oncology (2024) 35 (suppl_2): S428-S481.

CONTEXTUALIZACIÓN
Colon Localizado Inestable MSI-H ¿inmuno?

NICHE-2
(n:115)

Seguro: 98% van a qx sin retrasos
Respuesta patológica en 98%
- ≤10% células viables:95%
- pRC :68%

4% efectos 2º g3-4, **cualquier grado de iAE 63%**

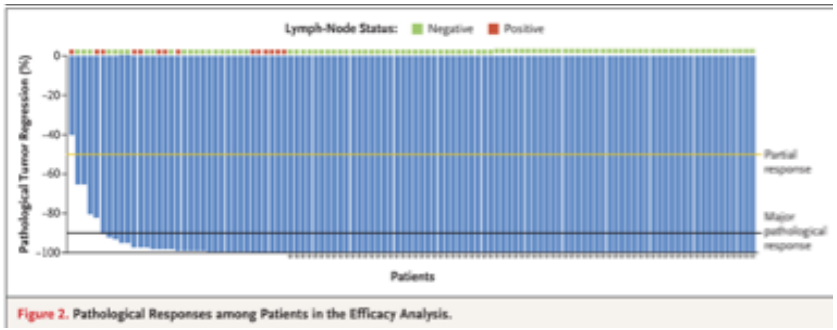
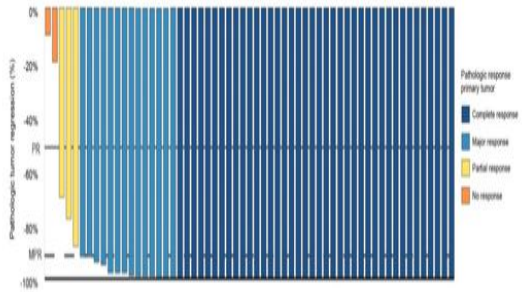


Figure 2. Pathological Responses among Patients in the Efficacy Analysis.

NICHE-3
(n:59)

Primary endpoint was met with a pathologic response observed in 57/59 (97%) patients
Of which 92% major pathologic responses and 68% pathologic complete responses



Ef Adv g3-4:10%
Algún E.Adv :80% (endocrinopatías)

pCR 68%
La misma que NICHE-2

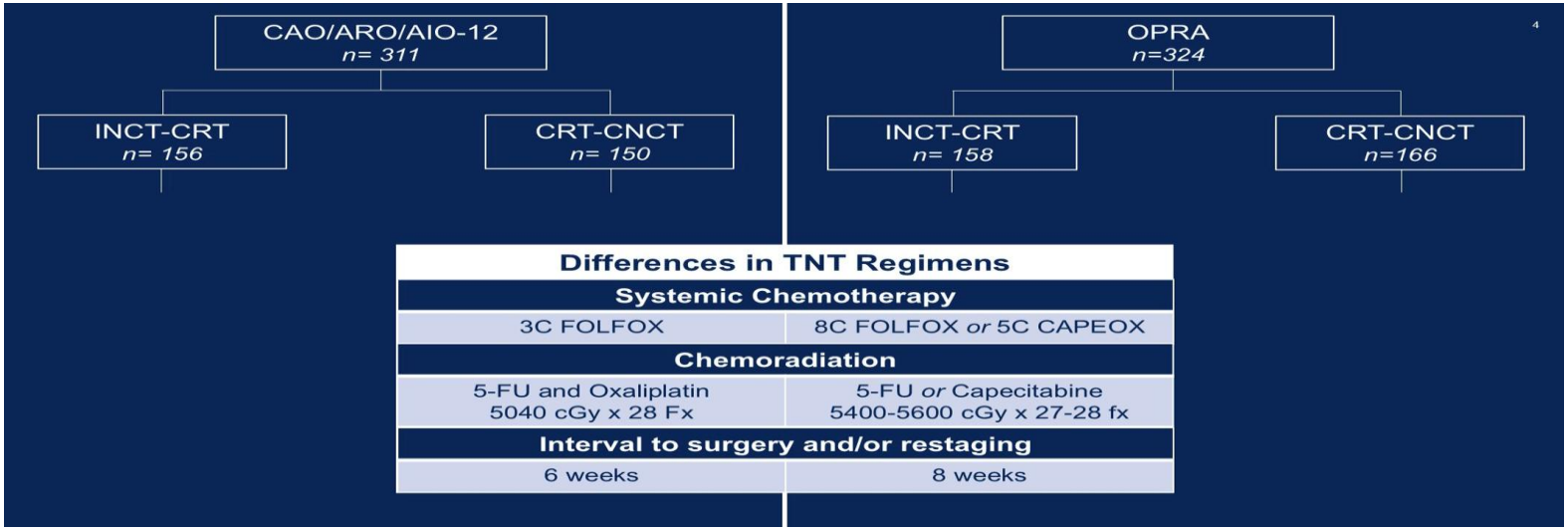
Con un seguimiento de 8 meses:

todos vivos y 98% libres de enfermedad

Chalabi M, C N Engl J Med. 2024 Jun 6;390(21):1949-1958. &Chalabi. Annals of Oncology (2024) 35 (suppl_2): 1-72.&P.G.M. de Gooyer of Oncology (2024) 35 (suppl_2): S428-S481.

Cáncer de Recto:
Análisis combinado CAO/ARO/AIO-12 y OPRA

Esquemas diferentes



Población con estadio II/III de cáncer de recto, recibe **tto de inducción o consolidación con QT/RDT**

Objetivo 1º:SLE

Objetivos 2º: recurrencia a distancia, recurrencia local y SG

Williams. ASCOGI2025. Abstract21

Cáncer de Recto:
Análisis combinado CAO/ARO/AIO-12 y OPRA

Esquemas diferentes

Watch and Wait vs. Total Mesorectal Excision in patients with rectal cancer with a complete or near complete response to total neoadjuvant therapy: *Pooled Analysis of the CAO/ARO/AIO-12 and OPRA Trials*

Población con estadio II/III de cáncer de recto, recibe **tto de inducción o consolidación con QT/RDT**

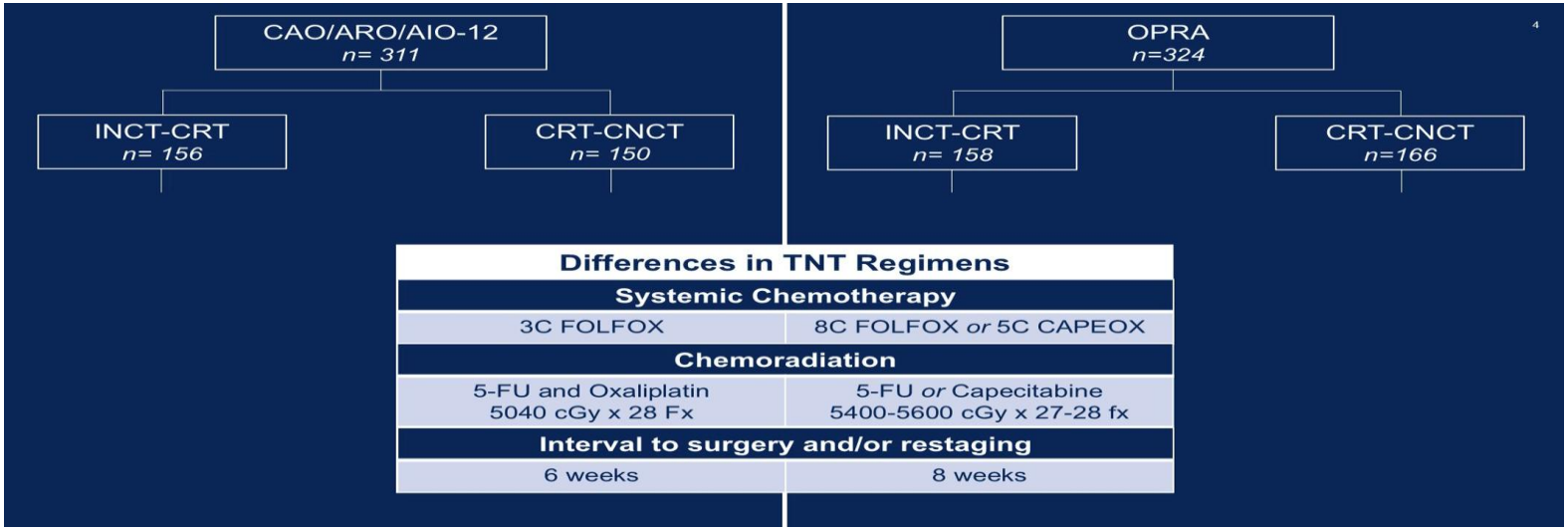
Objetivo 1º:SLE

Objetivos 2º: recurrencia a distancia, recurrencia local y SG

Williams. ASCOGI2025. Abstract21

Cáncer de Recto:
Análisis combinado CAO/ARO/AIO-12 y OPRA

Esquemas diferentes

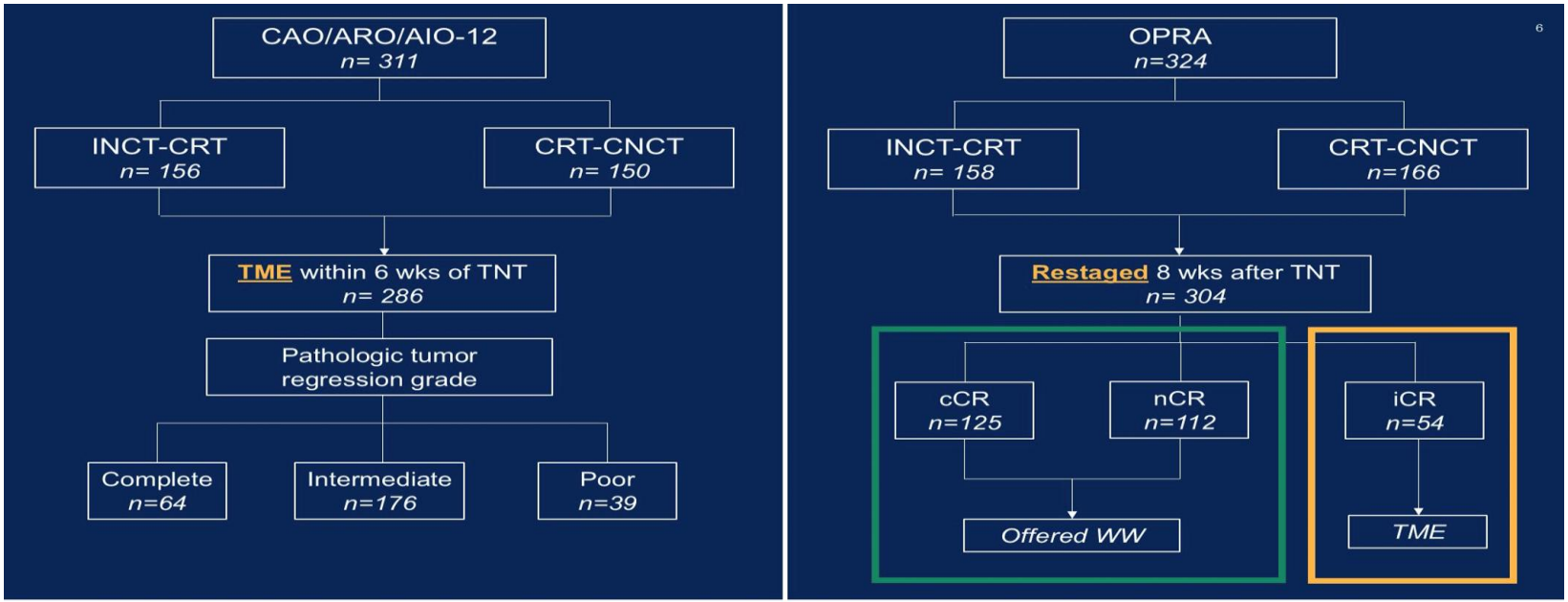


OPRA da 2,5 meses más de QT sistémica, más dosis de RDT y más intervalo desde el final de TNT a la estadificación

Williams. ASCOGI2025. Abstract21

Cáncer de Recto: **Análisis combinado CAO/ARO/AIO-12 y OPRA**

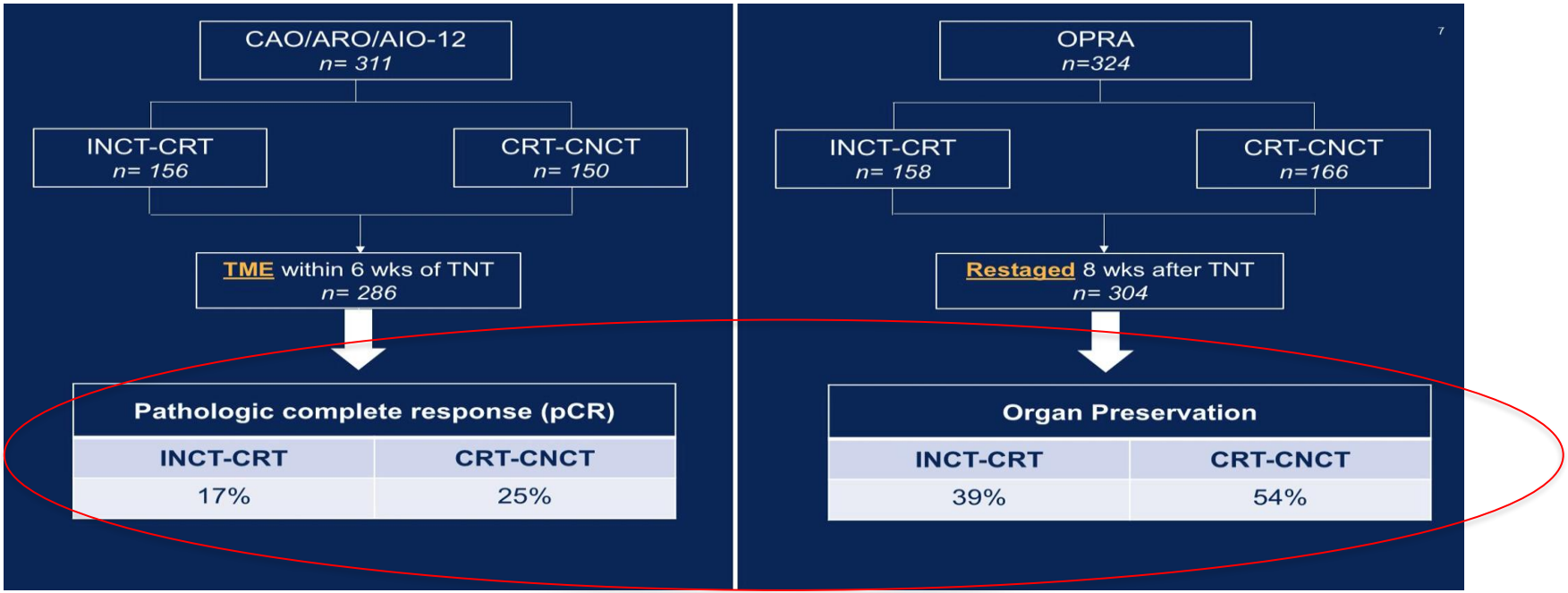
Flow Chart



Williams. ASCOGI2025. Abstract21

Cáncer de Recto: **Análisis combinado CAO/ARO/AIO-12 y OPRA**

Mensaje sobre inducción o consolidación



La Radioterapia Primero…..

Williams. ASCOGI2025. Abstract21

Cáncer de Recto: **Análisis combinado CAO/ARO/AIO-12 y OPRA**

Ccas basales: disbalance ligero

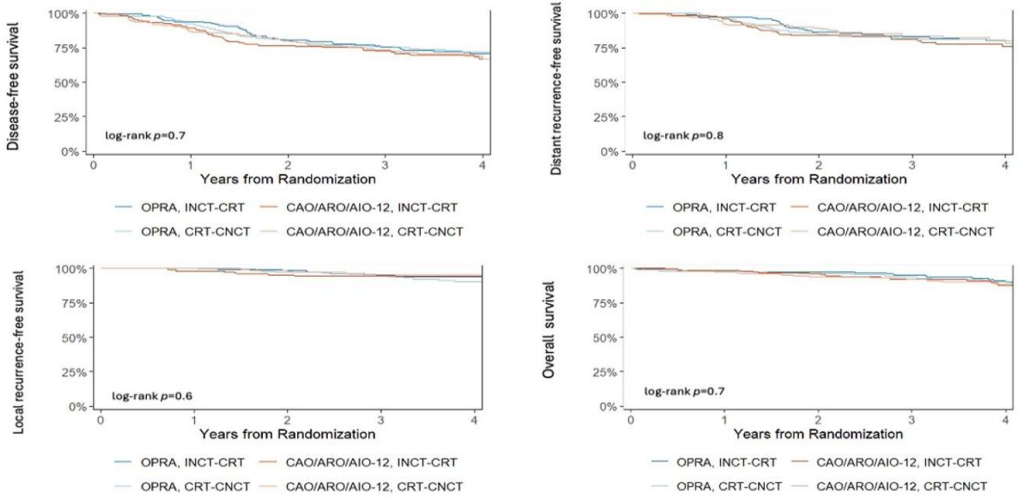
Variable	OPRA n = 324	CAO/ARO/AIO-12 n = 304	p-value
Median age, year (IQR)	58 (50, 67)	61 (54, 68)	***<0.001***
Female, No (%)	119 (37)	100 (33)	0.3
ECOG performance status, No. (%)			0.8
0	232 (72)	217 (73)	
1 or 2	91 (28)	81 (27)	
cT category No. (%)			***0.002***
cT1 or 2	32 (9.9)	9 (3)	
cT3	250 (77)	250 (82)	
cT4	42 (13)	45 (15)	
cN category No. (%)			***<0.001***
cN-negative	94 (29)	29 (9.8)	
cN-positive	230 (71)	268 (90)	
Median tumor distance from AV, cm (IQR)	4.40 (3.00, 6.50)	6.00 (4.00, 9.00)	***<0.001***
High-grade tumor histology, No. (%)	15 (4.6)	18 (5.9)	0.4

Williams. ASCOGI2025. Abstract21

Cáncer de Recto: **Análisis combinado CAO/ARO/AIO-12 y OPRA**

No hay diferencias en diferentes ítems (“quitado o no el recto”)

Survival outcomes by study and treatment arm



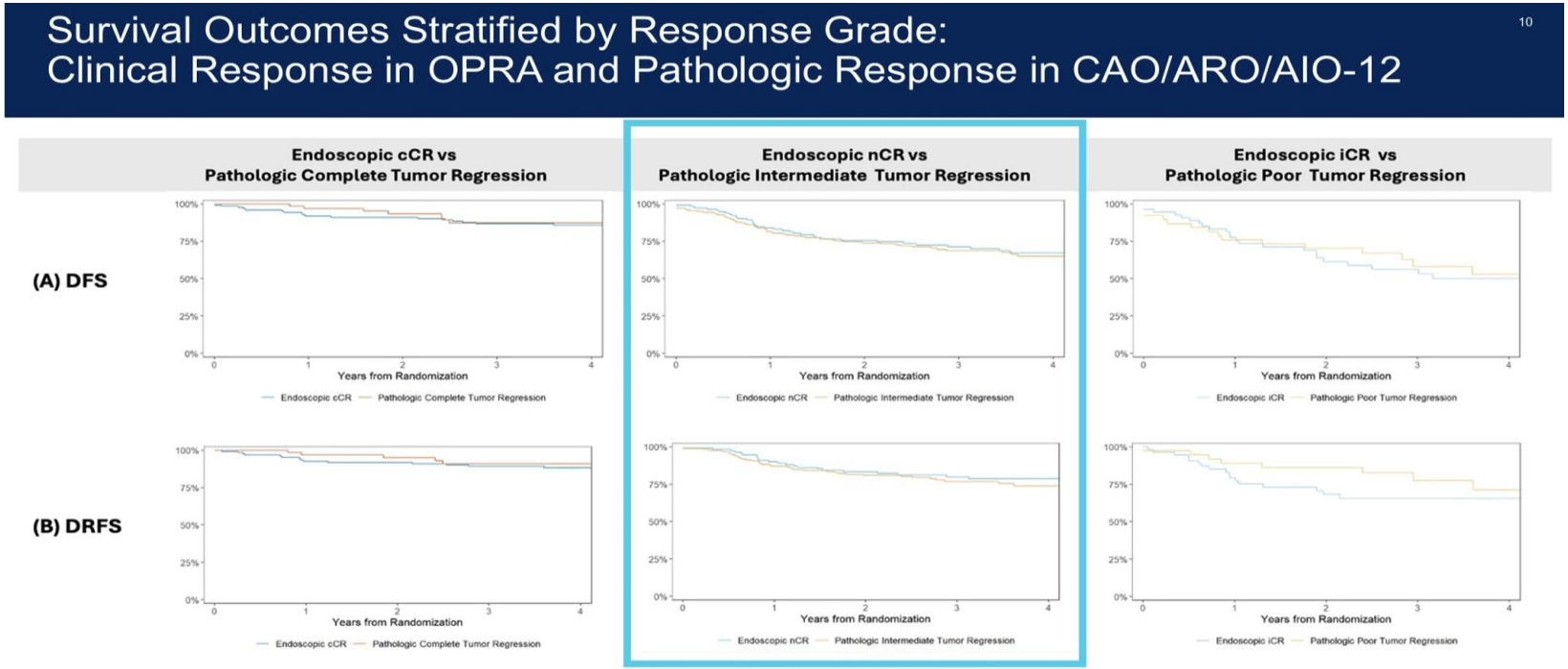
3-year Survival Outcomes

	CAO/ARO/AIO-12	OPRA
DFS	73 (71-81%)	76 (68-78%)
DRFS	82 (78-87%)	82 (78-87%)
LRFS	95 (92-98%)	95 (92-97%)
OS	92 (89-95%)	94 (89-95%)

Williams. ASCOGI2025. Abstract21

Cáncer de Recto: **Análisis combinado CAO/ARO/AIO-12 y OPRA**

No hay diferencias en diferentes ítems (“quitado o no el recto”)



Williams. ASCOGI2025. Abstract21

Cáncer de Recto: **Análisis combinado CAO/ARO/AIO-12 y OPRA**

Conclusión

Key Takeaway Points/Conclusions

A selective watch-and-wait strategy is a safe treatment option in patients with a complete or near complete response to TNT

- There were no differences in oncologic outcomes between patients treated with TNT and mandatory TME (CAO/ARO/AIO-12) or a selective WW strategy (OPRA)
- More than six weeks of systemic chemotherapy (3C FOLFOX) does not appear to improve survival in stage II/III rectal cancer patients treated with chemoradiation
- Patients with a near-complete clinical response after neoadjuvant therapy are still eligible for watch-and-wait surveillance, as this group has equivalent survival to patients with intermediate tumor regression after mandatory TME

Williams. ASCOGI2025. Abstract21

CONCLUSIONES

1. **Tratamiento en 1L dirigido por biomarcador**: MSI-H y BRAF V600E mutados, cambio en el 1L con nivo/ipi y probablemente enco/cetu y FOLFOX (esperamos SG).

2. **Biopsia Líquida:** marca su positividad riesgo de recurrencia, cambia el manejo de 1 de cada 6, el aclaramiento es pronóstico, solo se benefician de adyuvancia los positivos

3. En **colon refractario** sin mx hepáticas ¿BOT/BAL en un futuro?

4.Enfermedad **Localizada Inestable** ¿manejo diferente?

5. Recto sometido a tto TNT :consolidación mejor, si hay respuesta no es necesario ¿operar?

¡Muchas gracias!!!!

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