



GRUPO ESPAÑOL MULTIDISCIPLINAR  
EN CÁNCER DIGESTIVO

# Newsletter

Julio 2023



GRUPO ESPAÑOL MULTIDISCIPLINAR  
EN CÁNCER DIGESTIVO

**COLON**

**ESTUDIOS  
EN MARCHA**



GRUPO ESPAÑOL MULTIDISCIPLINAR  
EN CÁNCER DIGESTIVO

**GEMCAD 1401 | EPA-SP: Estudio observacional para evaluar la eficacia del uso inicial vs diferido de las terapias dirigidas, en cáncer de colon metastásico. Coordinadores: Dres. Maurel, Feliu, García-Albéniz.**

## ESTADO DEL ESTUDIO

- Aceptado para poster en Congreso ASCO 2023



Abstract ID: 3597

# Upfront vs. deferred monoclonal antibodies in metastatic colorectal cancer. A target trial emulation using the GEMCAD 14-01 prospective cohort

Joan Maurel<sup>1,2</sup>, Helena Oliveres<sup>3,4</sup>, Vicente Alonso-Orduna<sup>5</sup>, Jaime Feliu<sup>6</sup>, Ana Fernandez-Montes<sup>4</sup>, Marta Martín-Richard<sup>5</sup>, Elisa Galvez-Munoz E<sup>8</sup>, Ana Ruiz-Casado A<sup>7</sup>, Alfonso Yubero-Esteban<sup>9</sup>, Jorge Aparicio<sup>2</sup>, Julia Alcaide-García<sup>10</sup>, Javier Gallego Plazas<sup>11</sup>, Alberto Carmona-Bayonas<sup>12</sup>, Carlos Fernandez-Martos<sup>11</sup>, Rosa Gallego-Sánchez<sup>13</sup>, Hermíni Manzano<sup>14</sup>, Ruben Leno<sup>15</sup>, Miriam Cuatrecasas<sup>12</sup>, Xabier Garcia-Albeniz<sup>16,17</sup>

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## 1. Background

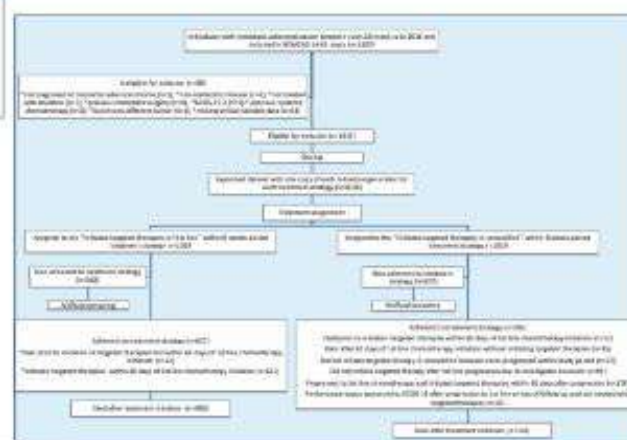
There are no randomized trials comparing the addition monoclonal antibodies (MAB: bevacizumab, cetuximab, panitumumab) to first line chemotherapy (upfront use) versus deferring their addition to the second-line chemotherapy (deferred use) in patients with metastatic colorectal cancer (mCRC). The potential advantage of the upfront use is to prolong progression free-survival, whereas the advantage of a deferred use would be a decreased exposure to drug toxicity while maintaining their effect on overall survival. We emulated a target trial comparing upfront vs deferred use of MAB using the GEMCAD 14-01 observational registry.

## 2. Methods

We first specified the (hypothetical) target trial to fully articulate the research question and then emulated it using real-world data. The eligibility criteria of the target trial were a diagnosis of mCRC, being treatment naive, and a ECOG PS  $\leq 2$ . The target trial would randomize patients to the following strategies: (1) initiation of MAB within 2 months of starting first line chemotherapy ("upfront MAB") and (2) initiation of MAB within 2 months of starting second line chemotherapy ("deferred MAB"). The primary outcome of the target trial would be overall survival and the causal contrast (or estimand) would be the effect under complete adherence. We emulated this target trial using data from the GEMCAD 1401 registry (ClinicalTrials.gov identifier: NCT02254941), which collected data prospectively from 47 Spanish centers from June 2014 to June 2018. The emulation used the same definitions of eligibility criteria and treatment strategies, and classified individuals according to their baseline data using clones. The effect under complete adherence was estimated by censoring patients when they deviated from the assigned treatment strategy and by using time-varying weights to adjust for baseline and post-baseline confounding.

## 3. Results

3.1. Flow diagram of individual patients with advanced colorectal cancer included to GEMCAD 1401 trial

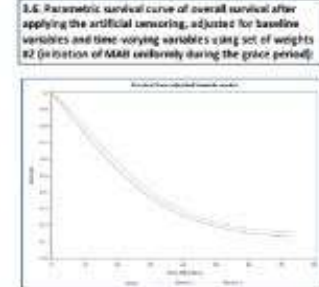
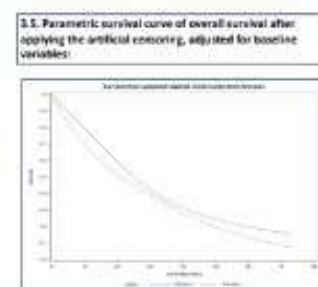
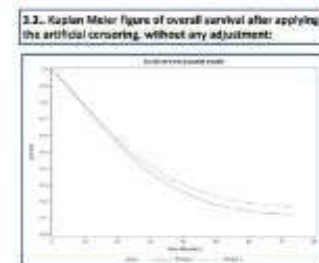
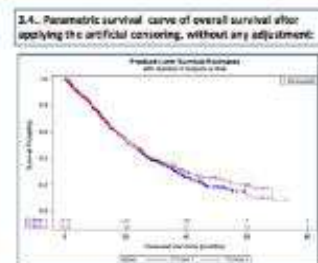


3.2. Baseline Characteristics

Characteristic	Upfront MAB (n=100)	Deferred MAB (n=100)
Age, mean (SD)	62.4 (10.1)	62.1 (10.2)
Sex, n (%)		
Male	58 (58)	57 (57)
Female	42 (42)	43 (43)
Race, n (%)		
White	95 (95)	94 (94)
Black	3 (3)	4 (4)
Hispanic	2 (2)	2 (2)
Asian	0 (0)	0 (0)
Other	0 (0)	0 (0)
ECOG PS, n (%)		
0	15 (15)	14 (14)
1	45 (45)	46 (46)
2	40 (40)	40 (40)
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99	0 (0)	0 (0)
100	0 (0)	0 (0)

3.7. Effect estimates with different levels of adjustment - bootstrap

Outcome	Adjustment	HR (95% CI)	P-value
Overall survival	Unadjusted	0.95 (0.78 - 1.15)	0.62
	Adjusted	0.92 (0.75 - 1.12)	0.35
Progression-free survival	Unadjusted	0.98 (0.82 - 1.16)	0.88
	Adjusted	0.95 (0.79 - 1.14)	0.60
Quality of life	Unadjusted	1.02 (0.85 - 1.21)	0.82
	Adjusted	1.00 (0.84 - 1.19)	0.95
Health-related quality of life	Unadjusted	1.01 (0.84 - 1.20)	0.90
	Adjusted	0.99 (0.83 - 1.18)	0.98



## 4. Conclusions

Our study suggests little or no survival detrimental effect of deferring the use of MAB to the second line of treatment compared with the use of MAB as part of the first line of treatment among patients with mCRC.



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## GEMCAD 1802 - Estudio fase II aleatorizado y multicéntrico de FOLFOX6m + Ac monoclonal (anti-EGFR o bevacizumab) sólo o en combinación con quimioembolización hepática (Lifepearls-Irinotecan) en pacientes con cáncer colorrectal y enfermedad metastásica limitada al hígado con criterios de mal pronóstico.

Coordinadores: Dr. Maurel / Dr. Páez

Laboratorio colaborador: TERUMO / CRO: MFAR

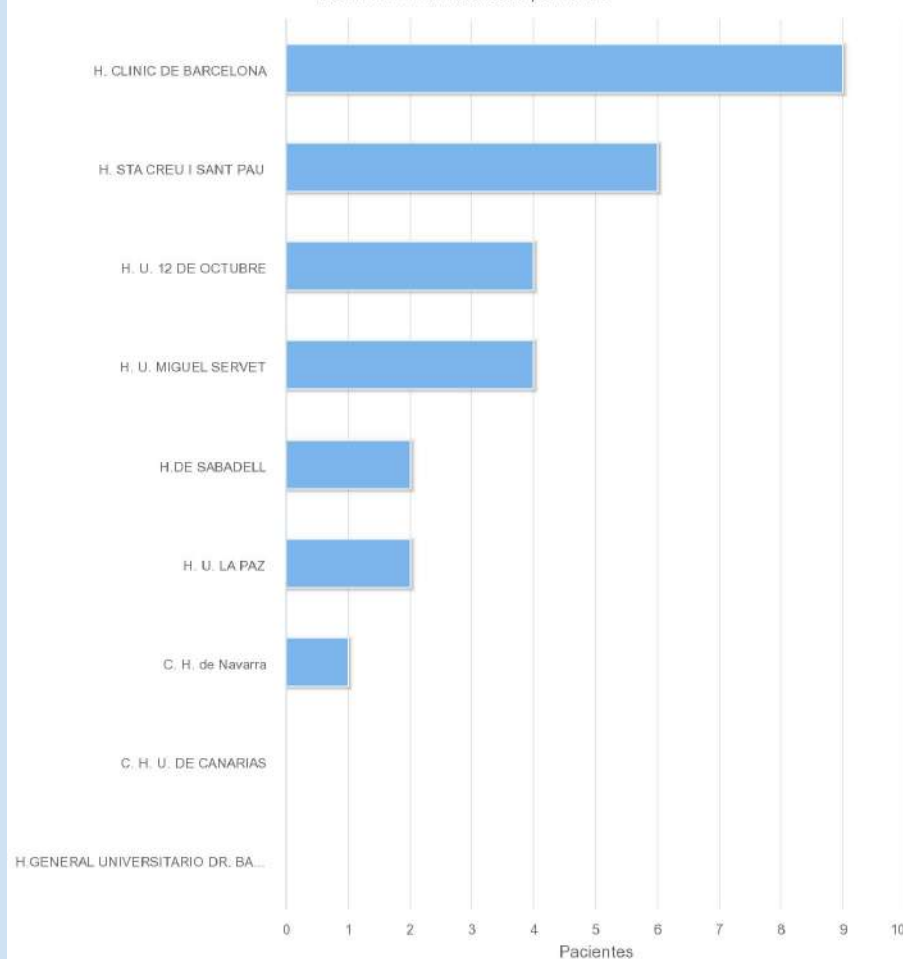
### Centros participantes:

### Pacientes incluidos:

1. Hospital Clínic de Barcelona Dr. Joan Maurel	9
1. Hospital de la Santa Creu i Sant Pau Dr. David Páez López-Bravo	6
1. Hospital Universitario La Paz Dr. Ismael Ghanem Cañete	2
1. Hospital de Sabadell Dr. Ismael Macías Declara	2
1. Hospital Universitario 12 de Octubre Dra. M. Carmen Riesco Martínez	4
1. Complejo Hospitalario de Navarra Dra. Ruth Vera García	1
1. Hospital Universitario de Canarias Dra. R. Hernández San Gil	-
1. Hospital U. de Alicante Dr. Bartomeu Massuti	-
1. Hospital Miguel Servet Dr. Vicente Alonso	5

- Pacientes incluidos: 29
- De los 29 pacientes incluidos hay 12 pacientes asignados al brazo experimental.
- Actualmente se está desarrollando la **ETAPA 1** del ensayo clínico en la que se realizará un análisis de futilidad.
- Se está trabajando en una **modificación del tamaño muestral** del ensayo clínico (reducción), que se presentará a través de una enmienda relevante.

Distribución individualizada por centro





GRUPO ESPAÑOL MULTIDISCIPLINAR  
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## GEMCAD 2102 / PEMBROLA - Phase II trial of Pembrolizumab and Olaparib in homologous-recombination deficient (HRD) advanced colorectal cancer (CRC)./ PEMBROLA

Coordinadores: Dra. García Carbonero / Dra. Riesco

Laboratorio colaborador: MSD /CRO: MFAR

	<b><u>CENTROS PARTICIPANTES</u></b>
1	<b>H.U. 12 de Octubre</b>
2	H. U. Marqués de Valdecilla
3	Hospital de la Santa Creu i Sant Pau
4	Hospital Universitario A Coruña (CHUAC)
5	Hospital Clínic de Barcelona
6	H.U. Virgen del Rocío (Sevilla)
7	H.U. Parc Taulí
8	Hospital Arnau de Vilanova (Lleida)
9	Institut Valencia d'Oncologia (IVO)
10	Hospital Universitario Vall d'Hebron
11	H. U. Miguel Servet
12	Hospital General Universitario de Elche
13	Hospital Clínico Universitario de Valencia
14	H. U. y Politécnico la Fe de Valencia

- Se ha firmado el acuerdo GEMCAD/MSD que garantiza la factibilidad del estudio
- Se ha presentado a AEMPS y CEIm en enero 2022, se espera la aprobación en breve.
- Primera visita de inicio realizada el 07Jul2022.
- Se ha realizado la SIV en todos los centros participantes.
- Ha firmado la HIP-CI el primer paciente en el estudio el 14Sep2022 en el H Sant Pau.
- Primer paciente incluido en el H U Miguel Servet el 22Dic2022.
- Se han incluido dos pacientes en el ensayo clínico.



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# ESTUDIOS TRASLACIONALES

**Traslacional en muestras GEMCAD 1401. Colaboración con Ajay Goel y Louis Vermoulen**

**Traslacional en muestras PULSE/POSIBA**

**Traslacional Beyond**



GRUPO ESPAÑOL MULTIDISCIPLINAR  
EN CÁNCER DIGESTIVO

**RECTO/CANAL ANAL**

**ESTUDIOS  
EN MARCHA**





GRUPO ESPAÑOL MULTIDISCIPLINAR  
EN CÁNCER DIGESTIVO

**GEMCAD 1601 | PIER** Preoperative Induction Therapy with 12 weeks of panitumumab in combination with mFOLFOX-6 in an enriched population (Quadruple Wild-Type) of patients with mrT3 rectal cancer of the middle third with clear mesorectal fascia PIER Trial.

Coordinador: Dr. Fernández Martos

## CENTROS PARTICIPANTES

Todos cerrados a fecha 07.03.2022

1. IVO
2. C.S. Parc Taulí
3. H. Clinic i Provincial
4. C. H. de Navarra
5. H. Gral. Univ. Elche
6. H. Univ. La Paz
7. H. Sta. Creu i Sant Pau
8. H. Univ. Vall d'Hebrón
9. H. Politécnico Univ. La Fe
10. H. Gral. Univ. Valencia
11. H. Univ. Virgen del Rocío
12. H. Sant Joan Despí-Moisés Broggi

## STATUS DEL ESTUDIO

- Manuscrito escrito y finalizado, en revisión por revista



GRUPO ESPAÑOL MULTIDISCIPLINAR  
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# GEMCAD 1703 / DUREC Phase II study of Durvalumab plus Total Neoadjuvant Therapy (TNT) in locally advanced rectal cancer. Coordinador: Dr. Jaume Capdevila

Estudio aprobado.

Protocolo finalizado y Presentado a la AEMPS y al  
CEIm en fecha 23May2020.

Enmienda 1 al protocolo aprobada el 02Jun2020.

Enmienda 2 al protocolo aprobada el 27Jul2021.

Enmienda 3 al protocolo aprobada el 02Feb2022

Están abiertos 10 centros para la fase II. Se cerró el  
reclutamiento con la inclusión del sexto sujeto de la  
run-in phase el 14Jul2020. Se reabrió el reclutamiento  
para incluir a 3 pacientes más a la run-in phase, y se  
cerró nuevamente el 10Sep2020. Se reabrió el  
reclutamiento el 14May2021 para la fase II.

Inclusión 1r paciente: 18Dec2019.

N:60 (run-in phase: 6) Total pacientes incluidos: 61.

Reclutamiento cerrado.

Centros participantes: 10 (**pacientes activos: 0**)

- H. Vall d'Hebron: 6 pacientes
- IVO: 6 pacientes
- Hospital Universitario A Coruña: 2 pacientes
- Corporació Sanitària Parc Taulí: 7 pacientes
- H. Clínic Barcelona: 3 pacientes
- H. de Elche : 4 paciente
- H. Moises Broggi: 14 pacientes
- H. 12 Octubre: 4 pacientes
- H. Navarra: 4 pacientes
- Hospital Miguel Servet: 11 pacientes

Inclusión primer paciente: 18Dec2019



GRUPO ESPAÑOL MULTIDISCIPLINAR  
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# GEMCAD 2103 - TIRANUS Phase II study of Atezolizumab plus Tiraglololumab in combination with chemoradiotherapy in localized squamous cell carcinoma of the anal canal

Coordinador Dr. Capdevila. Laboratorio colaborador Roche.  
CRO: MFAR

## Estudio Aprobado por el CEIm y la AEMPS!!!

Negociación de contratos GEMCAD/Hospital, en curso.

Apertura primer centro: Hospital Vall d'Hebron 18/03/2023

Fecha inicio de ensayo: 28/03/2023

Inclusión primer paciente (firma CI): 29/03/2023

## Listado de centros participantes:

Hospital	Investigador	Status Contrato GEMCAD-Centro
Hospital Vall d'Hebron	Jaume Capdevila	Firmado
Hospital Universitario Son Espases	Mónica Guillot	Firmado
Hospital Arnau de Vilanova (Lleida)	Montse Pampols	En proceso de firmas.
ICO Hospitalet	Mercedes Martínez Villacampa	En trámite
Hospital Parc Tauli	Ismael Macías	Firmado
Hospital Universitario de Toledo	Ignacio García Escobar	Firmado
Hospital de la Santa Creu i Sant Pau	David Páez	Firmado
Hospital Universitario Miguel Servet	Eduardo Polo	Firmado
Hospital Universitario y Politécnico la Fe de Valencia	Jorge Aparicio Urtasun	En trámite
HU Puerta de Hierro Majadahonda	Ana Ruiz Casado	En trámite
Hospital Sant Joan Despi	Gemma Soler	Firmado
Complejo Asistencial Universitario de León	Carmen Castañon	Firmado
Hospital General Universitario de Valencia	Maria José Safont	Firmado
Hospital General de Ciudad Real	Juana Maria Cano Cano	En trámite
<b>Hospital 12 de Octubre</b>	<b>María del Carmen Riesco</b>	En trámite

\* Roche posicionará la medicación en los centros a partir del 20.MAR.2023

# ● Aceptado para poster en Congreso ASCO 2023



Poster: 324a

## Atezolizumab plus Tiragolumab in combination with chemoradiotherapy in localized squamous cell carcinoma of the anal canal: TIRANUS (GEMCAD-2103) trial

Jaume Capdevila<sup>1\*</sup>, Mónica Guillot<sup>2</sup>, Montse Pampols<sup>3</sup>, Mercedes Martínez Villacampa<sup>4</sup>, Ismael Macías<sup>5</sup>, Ignacio García Escobar<sup>6</sup>, David Paez<sup>7</sup>, Eduardo Polo<sup>8</sup>, Jorge Aparicio<sup>9</sup>, Ana Ruiz Casado<sup>10</sup>, Gemma Soler<sup>11</sup>, Carmen Castañón<sup>12</sup>, Alejandro García-Alvarez<sup>1</sup>, María José Safont<sup>13</sup>, Jorge Hernando<sup>14</sup>, Juana María Cano<sup>14</sup>, Begoña Navalpotro<sup>15</sup>, David Armario<sup>16</sup>, Guillermo Villacampa<sup>17</sup>

1. Medical Oncology Department, Vall Hebron University Hospital, Vall Hebron Institute of Oncology (VHIO), Barcelona, Spain. 2. Medical Oncology Department, Hospital Universitario Son Espases, Palma de Mallorca, Spain. 3. Medical Oncology Department, Hospital Arnau de Vilanova, Lleida, Spain. 4. Medical Oncology Department, Institut Català d'Oncologia (ICO) L'hospitalet, L'hospitalet de Llobregat, Spain. 5. Medical Oncology Department, Hospital Universitario Parc Taulí, Sabadell, Spain. 6. Medical Oncology Department, Hospital General Universitario de Toledo, Toledo, Spain. 7. Medical Oncology Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain. 8. Medical Oncology Department, Hospital Universitario Miguel Servet, Zaragoza, Spain. 9. Medical Oncology Department, Hospital Universitario y Politécnica la Fe de Valencia, Valencia, Spain. 10. Medical Oncology Department, HJ, Puerta de Hierro Majadahonda, Madrid, Spain. 11. Medical Oncology Department, Institut Català d'Oncologia (ICO) L'hospitalet, Hospital Sant Joan Despi, Barcelona, Spain. 12. Medical Oncology Department, Complejo Asistencial Universitario de León, León, Spain. 13. Medical Oncology Department, Consorcio Hospital General Universitario de Valencia, Valencia University, CIBERONC, Spain. 14. Medical Oncology Department, Hospital General de Ciudad Real, Ciudad Real, Spain. 15. Radiation Oncology Department, Vall Hebron University Hospital, Vall Hebron Institute of Oncology (VHIO), Barcelona, Spain. 16. Radiology Department, Vall Hebron University Hospital, Barcelona, Spain. 17. Oncology Data Science group (OdySsey), Vall Hebron Institute of Oncology (VHIO), Barcelona, Spain.

### Background

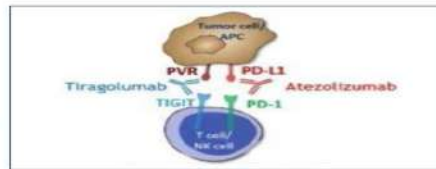
Radical chemoradiotherapy (CRT) is the standard of care in patients with localized anal squamous cell carcinoma; however, around 30% of patients do not achieve a complete clinical response (CCR) and require salvage surgery<sup>1,2</sup>.

Approximately 84% of anal carcinoma is associated with high risk types of human papilloma virus (HPV), primarily HPV 16 that generates high frequencies of tumor-infiltrating lymphocytes and inflammatory responses that have been linked with upregulation of PD-L1 (up to 74% of patients with squamous cell anal cancer)<sup>3-5</sup>.

Additionally, poliovirus receptor (PVR) expression has been described in several squamous cell carcinomas, and has been correlated with PD-L1 expression and poorer prognosis, suggesting dual inhibition of PVR and PD-L1 as a potential mechanism of overcome the resistance to immune checkpoint monotherapy (Fig.1)<sup>4,5</sup>. Moreover, CRT induces the generation of tumor-neoantigens and could act in synergy with immunotherapy in this setting.

The trial hypothesizes that the addition of atezolizumab (anti-PD-L1) and tiragolumab (anti-TIGIT) to chemoradiotherapy may lead to enhanced and more durable responses.

Figure 1. Atezolizumab and tiragolumab mechanism of action. Extracted from Rodríguez-Abreu et al ASCO 2020



### Key eligibility criteria

#### Inclusion

1. Histologically confirmed locoregional squamous cell carcinoma of the anal canal (stages I, II, IIIA, IIIB and IIIC).
1. Eligible for chemoradiotherapy.
2. At least one evaluable lesion.
3. Subjects  $\geq$  18 years old and ECOG 0-1 who sign informed consent.

#### Exclusion

1. Prior treatment for squamous cell carcinoma of the anal canal. Prior radiotherapy, chemotherapy or treatment with CD137 agonists or immune checkpoint blockade therapies, anti-CTLA-4, anti-TIGIT, anti-PD-1, and anti-PD-L1 are not allowed.
2. Allogenic transplant, autoimmune disease or immunodeficiency.
3. Systemic steroid therapy or any other form of immunosuppressive therapy within 14 days prior to the first dose of study treatment.
4. History of idiopathic pulmonary fibrosis, organizing pneumonia or pneumonitis.
5. Infections or vaccination within 4 weeks of first study dose.
6. Presence of uncontrolled intercurrent diseases.

### Sample size calculations

Using a precision analysis by Clopper-Pearson method (asymptotic 95% confidence interval) and an expected CCR rate of 85%, a total of 45 evaluable patients are needed to obtain a precision estimation of  $\pm 10.4\%$ .

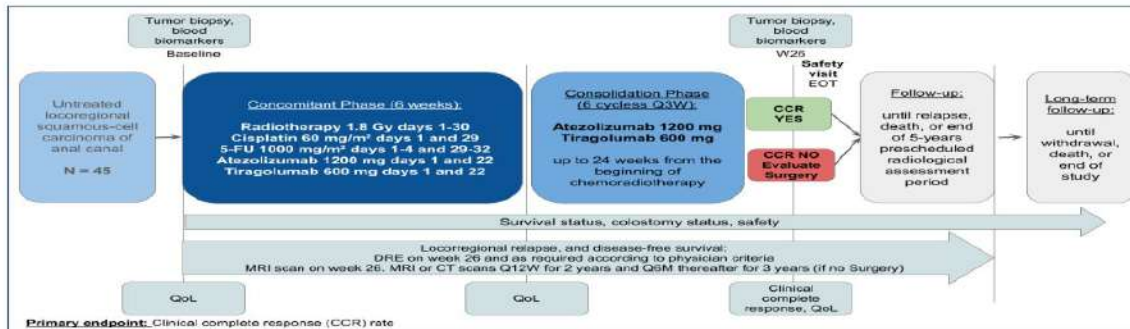


Figure 2. Study scheme

### Methods

TIRANUS is a Phase II, single-arm, open-label, non-randomized, multicenter clinical trial of atezolizumab and tiragolumab in concomitance with standard CRT as definitive therapy in treatment-naïve, localized squamous cell carcinoma of the anal canal (Fig.2).

Patients receive atezolizumab (1200mg) plus tiragolumab (600 mg) for 2 cycles (Q3W) in concomitance with the 6 weeks of CRT (cisplatin: 60 mg/m<sup>2</sup> on days 1 and 29; 5-FU: 1000 mg/m<sup>2</sup> per day on days 1-4 and 29-32; radiotherapy: 1.8 Gy per day / total dose 54 Gy). After the concomitant phase, patients receive atezolizumab (1200mg) and tiragolumab (600 mg) Q3W for 6 additional cycles (consolidation phase)(Fig.3).

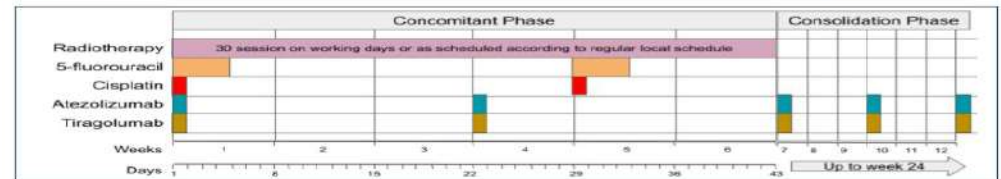


Figure 3. Treatment schedule

The primary endpoint is CCR rate, defined as the percentage of patients who achieve:

- a) radiological complete response (CR), disappearance of all lesions according to RECIST 1.1 criteria (locally assessed) and,
- b) no presence of residual disease assessed by biopsy at the end of consolidation phase (week 26).

Tumors response will be additionally scored by the Mandard tumour regression grading system. Secondary endpoints include Locoregional failure rate (LFR), Disease-free survival (DFS), Colostomy-free survival (CFS), Overall survival (OS), quality of life, safety and the determination of immune biomarkers potentially predictors of response in blood and tumor samples.



Accrual started in February 2023 and the first patient has already received the study treatment.

### References

1. Glynn-Jones R, Nilsson PJ, Aschele C, et al. Anal cancer: ESMO-ESSO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology* 2014.
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GRUPO ESPAÑOL MULTIDISCIPLINAR  
EN CÁNCER DIGESTIVO

## GEMCAD 2201 - GUARDANT REVEAL Circulating tumor DNA as complementary tool to assess response to neoadjuvant therapy in locally advanced rectal cancer

Coordinadores Dres. Yoelimar Guzmán, Borja de Lacy, José Ríos, Juan Ramón Ayuso, Joan Maurel

Pendiente abrir Centros

Laboratorio colaborador Guardant. CRO Mfar.

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# ESTUDIOS FINALIZADOS



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## GEMCAD 1903 - Estudio sobre el valor pronóstico de las duplicaciones de CYP2D6 y tratados Mit-5FU/RT: serie de validación (GEMCAD). Coordinador Dr. Feliu

### Serie de validación:

15 Centros participantes.

Se ha finalizado la recogida de muestras, que al final han llegado a 101. Las variaciones del CYP2D6 se han confirmado como factor pronóstico en la serie de la validación.

El artículo sobre este proyecto ya se ha publicado:

[Utility of CYP2D6 copy number variants as prognostic biomarker in localized anal squamous cell carcinoma.](#)

Trilla-Fuertes L, Gámez-Pozo A, Nogué M, Busquier I, Arias F, López-Campos F, Fernández-Montes A, Ruiz A, Velázquez C, Martín-Bravo C, Pérez-Ruiz E, Asensio E, Hernández-Yagüe X, Rodrigues A, Ghanem I, López-Vacas R, Hafez A, Arias P, Dapía I, Solís M, Dittmann A, Ramos R, Llorens C, Maurel J, Campos-Barros Á, Fresno Vara JÁ,

**Feliu J.**

[Cancer. 2023 Apr 25](#)

**Serie de diseño:  
58 casos**



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# NUEVAS PROPUESTAS

## Reveal Gemcad 2201

### **GEMCAD 2201 / GUARDANT REVEAL:**

Circulating tumor DNA as complementary tool to assess response to neoadjuvant therapy in locally advanced rectal cancer.

Dra. Yoelimar Guzmán - Servicio de Cirugía General y Digestiva, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain

Dr. Joan Maurel Santasusana - Servicio de Oncología, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain

**Estudio traslacional en estudio AZUR2. Coordinador Dr. Joan Maurel. (en elaboración).**

**Propuesta de estudio observacional comparativo tras tnt de preservación de órgano vs cirugía.**





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