I Jornada Regional

POST-ESMO

5 DE NOVIEMBRE DE 2025

LOGROÑO

# Cáncer colorrectal y Tumores neuroendocrinos

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# CANCER COLORRECTAL

# MRD & Adjuvant therapy

- DYNAMIC III (Plenary Session)
- PEGASUS (723O)

ctDNA is the best relapse biomarker, now we must prove it can guide treatment safely

# ctDNA-Guided Adjuvant Chemotherapy De-Escalation in Stage III Colon Cancer

**Stage III Colon Cancer**

- R0 resection
- ECOG 0 – 2
- Fit for at least a fluoropyrimidine (FP)
- Staging CT within 12 weeks
- Provision of adequate tumor tissue < 6 weeks post-operation
- No synchronous colorectal cancer

**Tumour-Informed ctDNA Analysis** (SaferSeqS[1] targeted CRC panel)

W5-6

R 1:1

**Clinicians nominate SoC Chemo**

**ctDNA-Informed Management**

- ctDNA-Negative → De-escalate
- ctDNA-Positive → Escalate

*1 cycle of pre-planned chemotherapy allowed prior to ctDNA-informed regimen*

**Pre-Planned SoC → De-escalation**

| |
|---|
| 6M FP → No chemo or 3M FP |
| 3M Oxaliplatin + FP → 3-6M FP |
| 6M Oxaliplatin + FP → 3M Oxaliplatin + FP or 6M FP |

*FP = fluoropyrimidine*

**Standard Management**

Treatment per clinician's choice (blinded to ctDNA result)

*Stratified by clinical risk (low vs high) and sites*

| Primary Analysis of ctDNA-Negative Cohort: Endpoints to be Presented Here | |
|---|---|
| Primary: 3-year recurrence-free survival (RFS) | Secondary: treatment adherence, safety |

Non-inferiority accepted if lower bound of one-sided 97.5% CI for difference at 3-years did not cross -7.5%

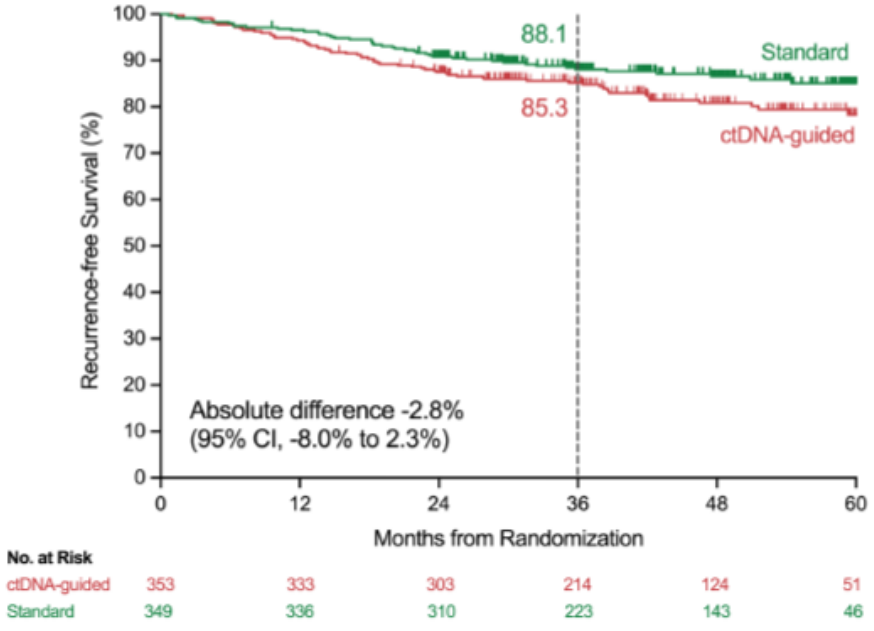
# POST-ESMO

| Treatment Information | | ctDNA-Informed De-Escalation N = 353, N (%) | | Standard Management N = 349, N (%) | |
|---|---|---|---|---|---|
| **Commenced per protocol treatment** | | **319 (90.4)** | | **347 (99.4)** | |
| **Chemotherapy received** | No Chemotherapy | 26 (7.4) | | 8 (2.3) | |
| | 3M Single agent FP | 119 (33.7) | **57.8%** | 1 (0.3) | **9.2%** |
| | 6M Single agent FP | 85 (24.1) | | 31 (8.9) | |
| | 3M Oxaliplatin doublet | 117 (33.1) | **34.8%** | 166 (47.6) | **88.6%** |
| | 6M Oxaliplatin doublet | 6 (1.7) | | 143 (41.0) | |

***RR: 0.41; P < 0.001***

**Primary endpoint not met**

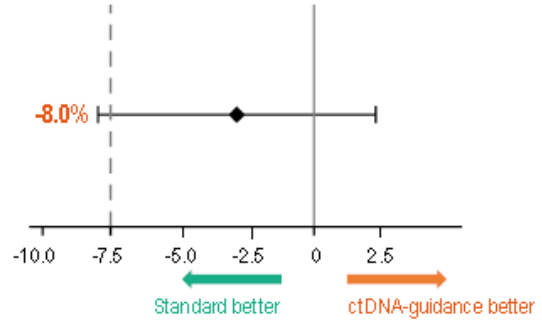
# Recurrence-Free Survival




**Median follow-up 47 months (0.68 - 67.0)**

| Arm | Total | Events | 3-year RFS (95% CI) |
|---|---|---|---|
| ctDNA | 353 | 63 | 85.3% (81, 89) |
| Standard | 349 | 45 | 88.1% (84, 91) |

**Absolute Difference in 3-year RFS (95% CI)**

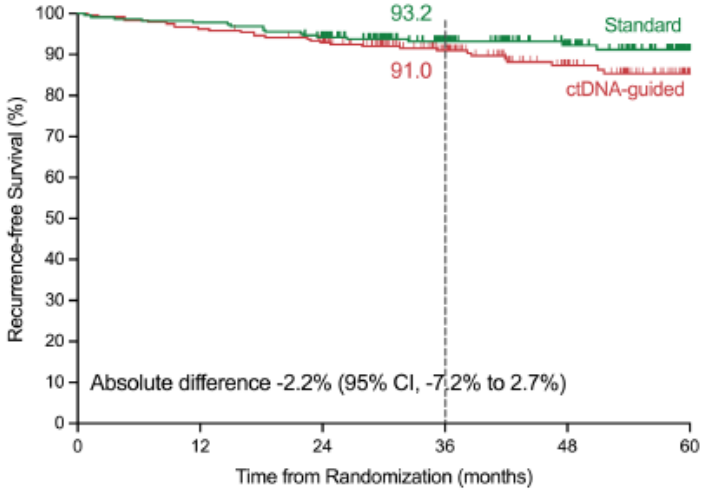


This was an exploratory, not pre-specified analysis.

**ctDNA-guided de-escalation appears safe, particularly in low-risk patients.**

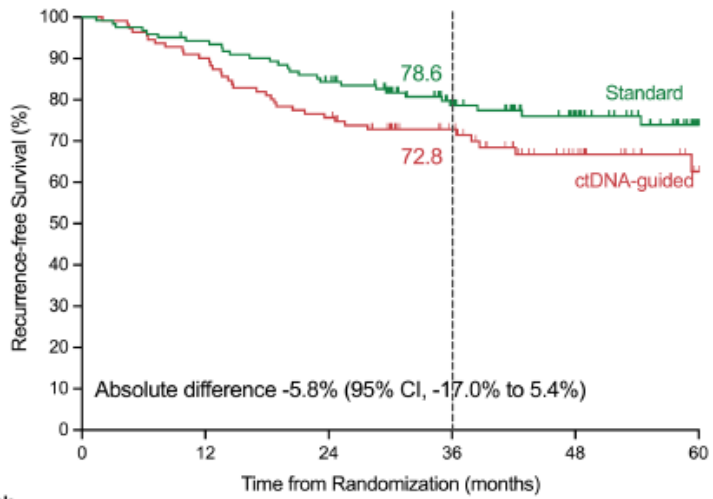
# RFS by Clinical Risk

## Clinical Low Risk (T1-3N1)




| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| ctDNA-guided | 242 | 233 | 219 | 160 | 93 | 39 |
| Standard | 227 | 222 | 209 | 152 | 95 | 32 |

## Clinical High Risk (T4 and/or N2)



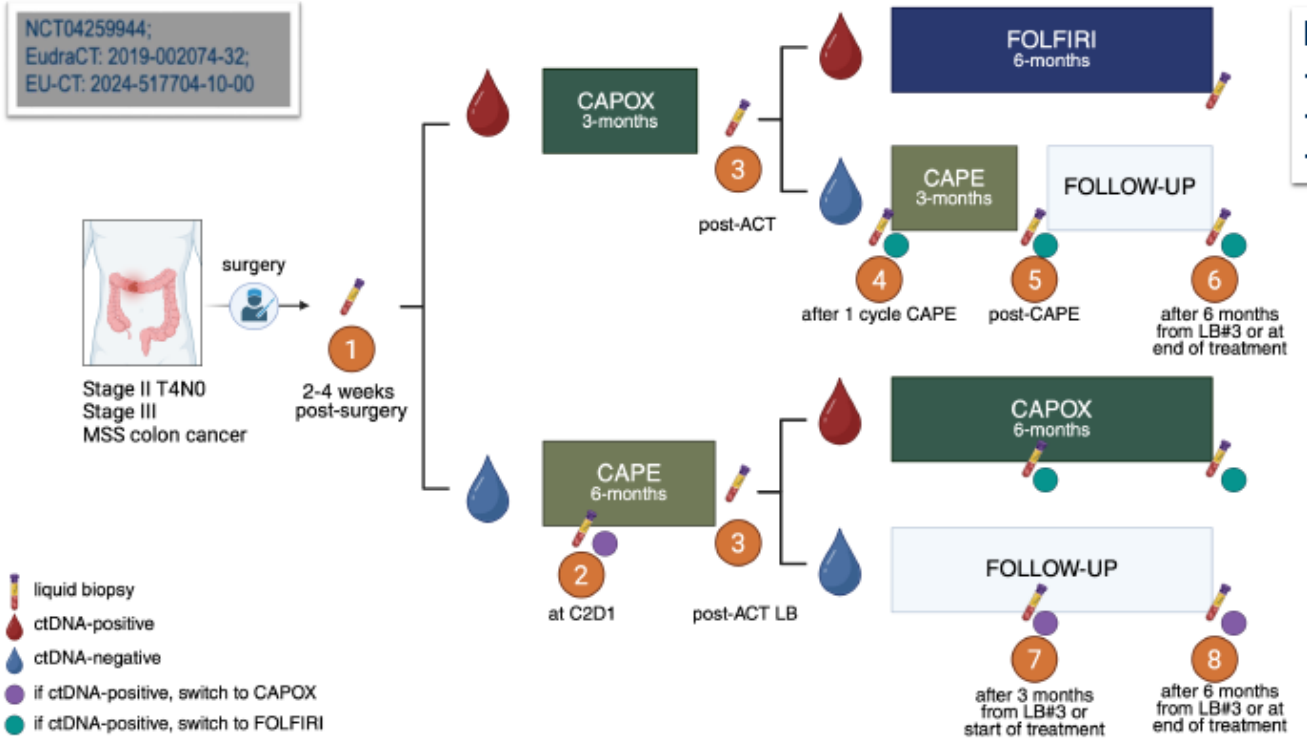

| No. at Risk | | | | | | |
|---|---|---|---|---|---|---|
| ctDNA-guided | 111 | 100 | 84 | 54 | 31 | 12 |
| Standard | 122 | 114 | 101 | 71 | 48 | 14 |

# Conclusions

## For patients with ctDNA-negative stage III colon cancer post-surgery

- Recurrence risk is low, with 3-year RFS of 87%
- ctDNA-informed treatment de-escalation was feasible with high adherence (90%)
  - Markedly reduced oxaliplatin exposure (88.6% → 34.8%)
  - Better safety profile: fewer treatment-related hospitalisations and grade ≥3 adverse events
  - Non-inferiority versus SoC was not confirmed, though outcomes were close (3-yr RFS 85.3% vs 88.1%), particularly in low-risk (T1-3N1) disease (3-yr RFS 91.0% vs 93.2%)
  - Could inform risk-benefit discussions for individual patients
- ctDNA-informed de-escalation strategies warrant further investigation

# Post-surgical liquid biopsy-guided treatment of stage III and high-risk stage II colon cancer patients: final results of the PEGASUS trial




**Primary endpoint**: relapse rate in patients with 2 consecutive negative ctDNA tests at 2 years

- Accrual 7/2020 – 7/2022
- Median follow-up: 42 mos.
- 135 patients treated
  - 35 ctDNA-positive
  - 100 ctDNA-negative
- Planned 134 ctDNA-negative not reached → reduced statistical power

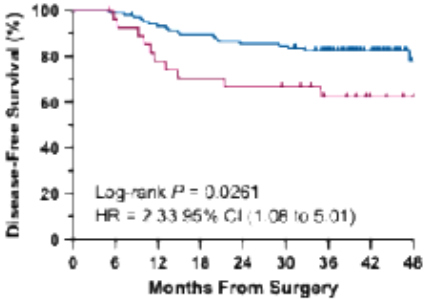
**Primary endpoint not met**

| | LB positive | LB negative |
|---|---|---|
| event free | 22 | 85 |
| relapsed | 13 | 15 |

Sensitivity: 46.4%
Specificity: 79.4%

- 100 ctDNA– patients → 12 relapses (2 local+10 distant) within 2 years
- 2-year recurrence-free rate: 88% (90% CI, 81–93)
- Primary endpoint not formally powered
- 2-year recurrence-free rate exceeded the 85% benchmarking, upper CI 93% crossed $H_1$ target 92% supporting clinical adequacy despite reduced power.

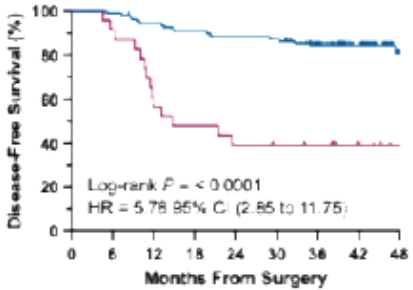
**ON –TREATMENT**
(LB3)




No at risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ctDNA Negative | 104 | 103 | 96 | 92 | 88 | 87 | 72 | 43 | 15 |
| ctDNA Positive | 28 | 26 | 21 | 19 | 18 | 17 | 13 | 9 | 6 |

**END OF TRETAMENT**
(LB3, LB5, LB6, LB8)




No at risk

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ctDNA Negative | 111 | 110 | 104 | 100 | 97 | 96 | 78 | 48 | 20 |
| ctDNA Positive | 24 | 21 | 13 | 11 | 9 | 8 | 7 | 4 | 1 |

| Parameter | Post-surgery | EoT |
|---|---|---|
| Sensitivity | ≈ 50% | ≈ 60% |
| Specificity | ≈ 80% | ≈ 95% |
| PPV | ≈ 45% | ≈ 75-80% |
| NPV | ≈ 85% | ≈ 90% |

# Immunotherapy in dMMR CRC

- FOxTROT vs NICHE-2 (724O)
- CheckMate 8HW (LBA29)

**Immunotherapy is curing patients, but we´re still defining when and how to use it**

# Comparison of outcomes in clinical trials of locally advanced dMMR colon cancer: data from the FOxTROT and NICHE-2 trials

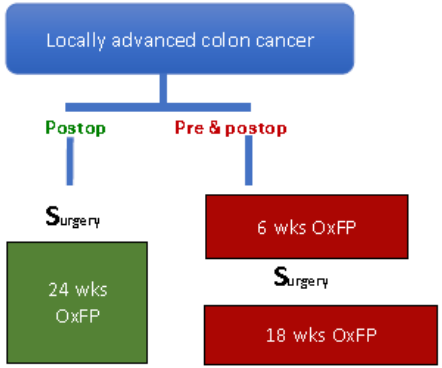
| | | | |
|---|---|---|---|
| Radiological T-stage | T3 | 120 (64.9%) | 22 (23.4%) |
| | T4 | 65 (35.1%) | 72 (76.6%) |
| Radiological N-stage* | N0 | 35 (19.3%) | 24 (25.5%) |
| | N+ | 146 (80.7%) | 70 (74.5%) |

## The FOxTROT & NICHE-2 Trial Designs

**Key Eligibility Criteria**

**FOxTROT**

- CT assessed cT3+, cN0-2
- No metastatic disease
- No clinical or radiological signs of obstruction



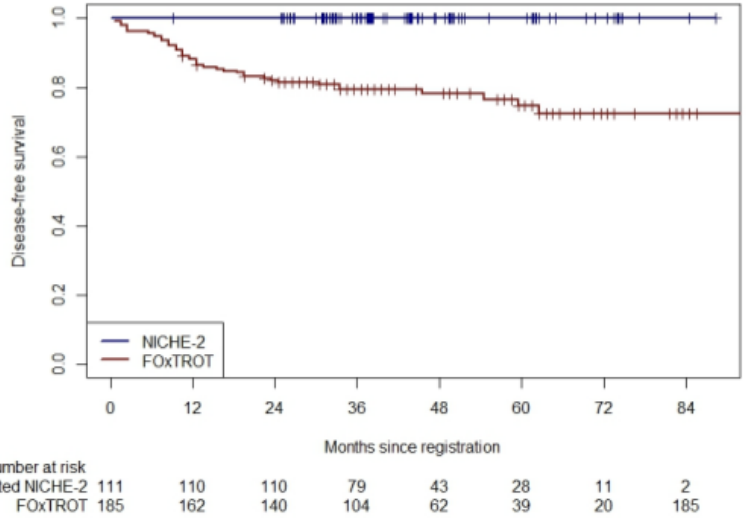

**NICHE-2**

- CT assessed cT3+ or N+
- No metastatic disease
- No clinical or radiological signs of obstruction
- Confirmed dMMR/ MSI-H status

| | | FOxTROT (peri-operative chemo) N=117* | NICHE-2 N=94** |
|---|---|---|---|
| Response (TRG) | Complete (TRG 1) | 5 (4.3%) | 68 (72.3%) |
| | Marked/ Mod (TRG 2-3) | 3 (2.6%) | 24 (25.5%%) |
| | Mild/None (TRG 4-5) | 107 (91.4%) | 1 (1.1%) |

# Primary analysis: 3 year Disease free survival

Neoadjuvant nivolimab and ipilimumab was superior to OxFp delivered before or after surgery




NICHE-2 (neoadjuvant nivolimab + ipilimumab)
DFS = 100%

FOxTROT (all strategies)
DFS = 80% (95%CI = 73-85%)

Log rank p<0.001

*No differences observed in DFS between the 2 FOxTROT strategies (p=0.9)*

This data further supports the use of neoadjuvant IO.

# Conclusions

- For comparably selected trial patients with dMMR LACC
  - Neoadjuvant nivolumab and ipilimumab resulted in statistically significant and clinically meaningful improvements in long term outcomes compared with chemotherapy strategies
  - No recurrences in NICHE-2 were observed despite the high proportion of T4 tumors
  - Low rate of pathological response with neoadjuvant chemotherapy in FOxTROT
  - Shorter treatment duration in NICHE-2
- Clinical staging identified poor prognostic dMMR patients in FOxTROT
- Highest gains with neoadjuvant IO are in clinically staged high risk (cT4) patients compared with chemotherapy
  - However 20% recurrence rate in T3 patients is highly clinically relevant
- This data further supports the use of neoadjuvant immunotherapy

**Limitations:**

- **Not a randomized comparison:** two independent trials.
- **Different designs and populations** (neoadjuvant IO vs peri-operative chemo)
- **Indirect analysis** (individual data from NICHE-2 + aggregated FOxTROT)
- **Possible selection bias** (confirmed dMMR = more favorable biology)
- **Immature follow-up**, few DFS events in NICHE-2

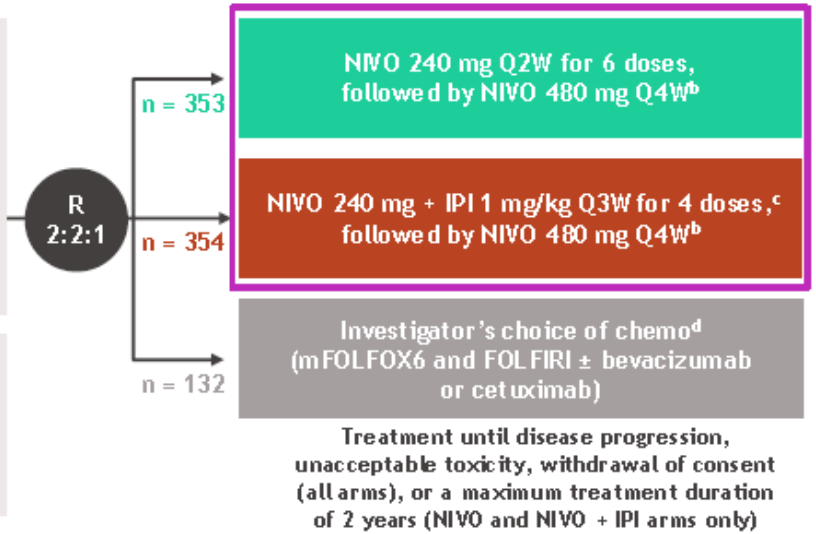
# Nivolumab plus ipilimumab vs nivolumab monotherapy for microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: new results from CheckMate 8HW

## Preplanned PFS final analysis for NIVO + IPI vs NIVO (1L) and the first interim analysis of OS for NIVO + IPI vs NIVO (all lines)

- CheckMate 8HW is a randomized, multicenter, open-label phase 3 trial[a]

**Key eligibility criteria:**
- Histologically confirmed unresectable or metastatic CRC
- MSI-H/dMMR status by local testing
- Immunotherapy-naïve
- ECOG PS 0 or 1

**Stratification factors:**
- Prior lines of treatment (0 vs 1 vs ≥ 2)
- Primary tumor location (right vs left)

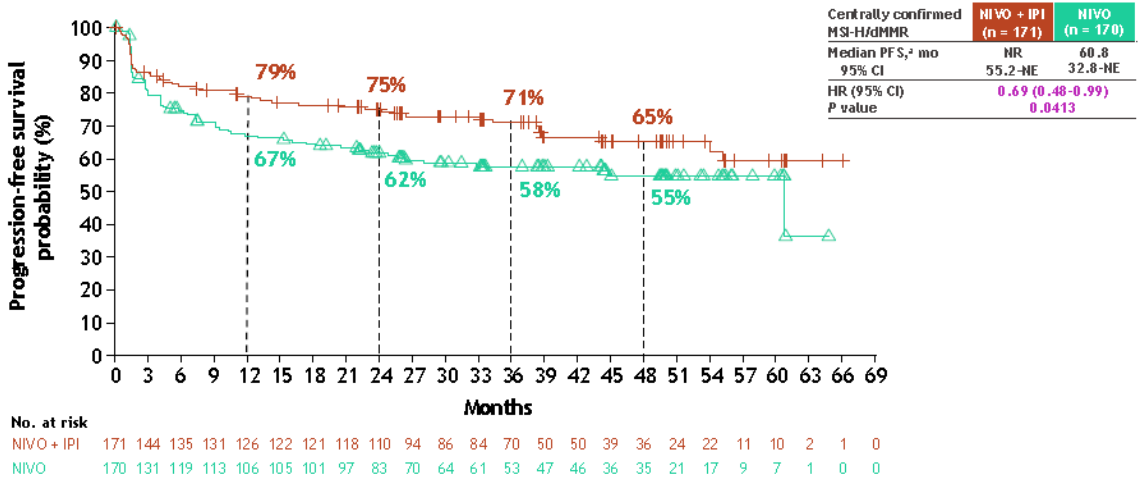



**Dual primary endpoints in patients with centrally confirmed MSI-H/dMMR status[e]:**
- PFS by BICR[f] (NIVO + IPI vs chemo in 1L)
- PFS by BICR[f] (NIVO + IPI vs NIVO across all lines)

**Secondary endpoints in patients with centrally confirmed MSI-H/dMMR status[e]:**
- PFS by BICR[f] (NIVO + IPI vs NIVO in 1L)
- ORR by BICR[f] (NIVO + IPI vs NIVO in 1L)
- OS (NIVO + IPI vs NIVO across all lines)
- ORR by BICR[f] (NIVO + IPI vs NIVO across all lines)

**Other key endpoints in 1L treated patients**
- Safety

# PFS: 1L NIVO + IPI vs NIVO in centrally confirmed patients




| Centrally confirmed MSI-H/dMMR | NIVO + IPI (n = 171) | NIVO (n = 170) |
|---|---|---|
| Median PFS,[a] mo | NR | 60.8 |
| 95% CI | 55.2-NE | 32.8-NE |
| HR (95% CI) | 0.69 (0.48-0.99) | |
| *P* value | 0.0413 | |

- In patients with centrally confirmed MSI-H/dMMR mCRC, 1L NIVO + IPI demonstrated clinically meaningful improvement in PFS vs NIVO (HR 0.69, [95% CI 0.48-0.99])
  - The prespecified threshold for statistical significance was not met ($P < 0.0383$)
  - These data are consistent with those observed in the 1L all randomized population by local testing (HR 0.75, [95% CI 0.56-1.01])

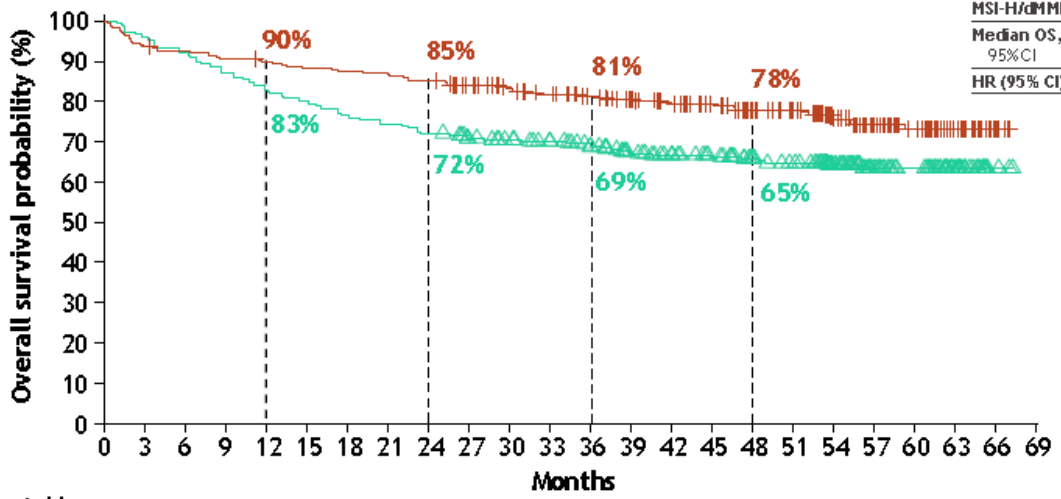
# ORR: 1L NIVO + IPI vs NIVO in centrally confirmed patients

| | NIVO + IPI (n = 171) | NIVO (n = 170) |
|---|---|---|
| ORR,[a,b] % | 73 | 61 |
| 95% CI | 65-79 | 53-79 |

**These new results further support NIVO + IPI as a standard of care option for the 1L treatment of MSI-H/dMMR mCRC.**

These new results further support NIVO + IPI as a standard of care option for the 1L treatment of MSI-H/dMMR mCRC.

# OS: NIVO + IPI vs NIVO across all lines in centrally confirmed patients




| Centrally confirmed MSI-H/dMMR | NIVO + IPI (n = 296) | NIVO (n = 286) |
|---|---|---|
| Median OS, mo | NR | NR |
| 95% CI | NE-NE | NE-NE |
| HR (95% CI) | 0.61 (0.45-0.83) | |

No. at risk

| | | | | | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| NIVO + IPI | 296 | 279 | 273 | 267 | 264 | 260 | 257 | 255 | 251 | 240 | 229 | 219 | 209 | 196 | 186 | 175 | 160 | 149 | 118 | 83 | 65 | 35 | 5 | 0 |
| NIVO | 286 | 275 | 263 | 252 | 238 | 228 | 220 | 213 | 207 | 195 | 189 | 182 | 172 | 157 | 148 | 139 | 127 | 122 | 102 | 63 | 50 | 23 | 3 | 0 |

- In patients with centrally confirmed MSI-H/dMMR mCRC, descriptive analyses indicated that OS favored NIVO + IPI vs NIVO across all lines (HR 0.61, [95% CI 0.45-0.83])
  - With ~69% of expected events observed (168 of ~243 expected deaths), OS data remain immature

# Targeted & Precision Approaches

- PARERE (LBA32)
- CITRIC (LBA33)

→ Rechallenge

- STELLAR-303 (LBA30)
- DESTINY-CRC02 (737MO)

→ Targeted Therapies

- AI-AtezoTRIBE and AVETRIC (725O) → AI

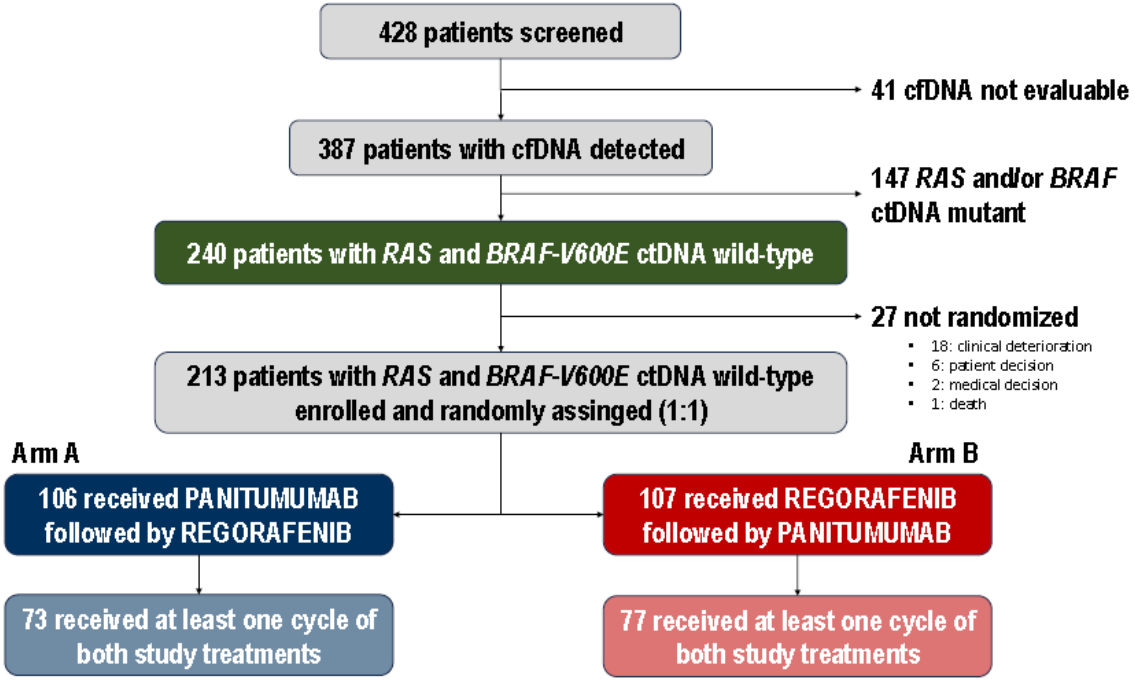
**Targeted therapy is expanding, but precision still needs validation.**

# Panitumumab retreatment followed by regorafenib versus the reverse sequence in chemorefractory metastatic colorectal cancer patients with *RAS* and *BRAF* wild-type circulating tumor DNA (ctDNA): Final results of the randomized PARERE trial by GONO

**Key Eligibility Criteria**

- ≥ 18 years of age
- ECOG PS ≤ 1
- Previous treatment with fluoropyrimidine, oxaliplatin, irinotecan and anti-angiogenics
- RAS/BRAF wild-type mCRC previously treated with a first-line anti-EGFR-containing regimen, with at least PR or SD for ≥ 6 months
- At least one intervening anti-EGFR-free line of therapy
- At least 4 months between the end of anti-EGFR administration and screening

*RAS/BRAF* ctDNA wild-type

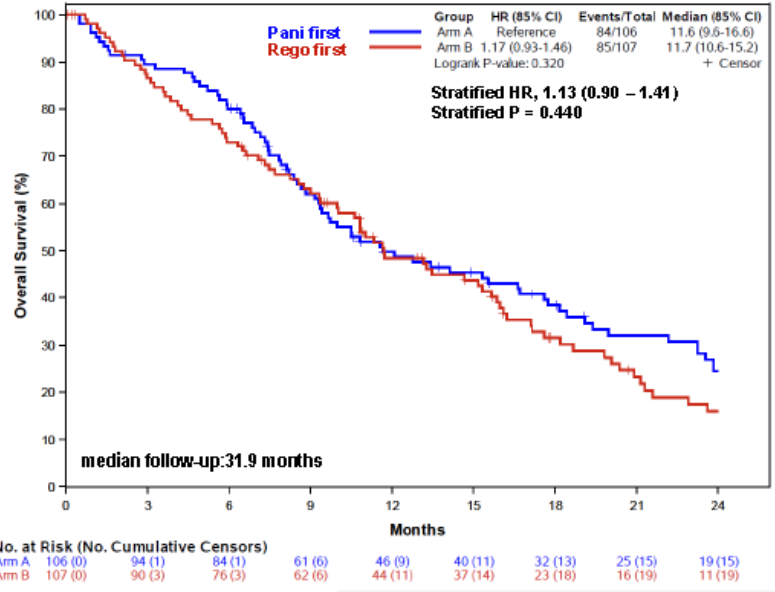


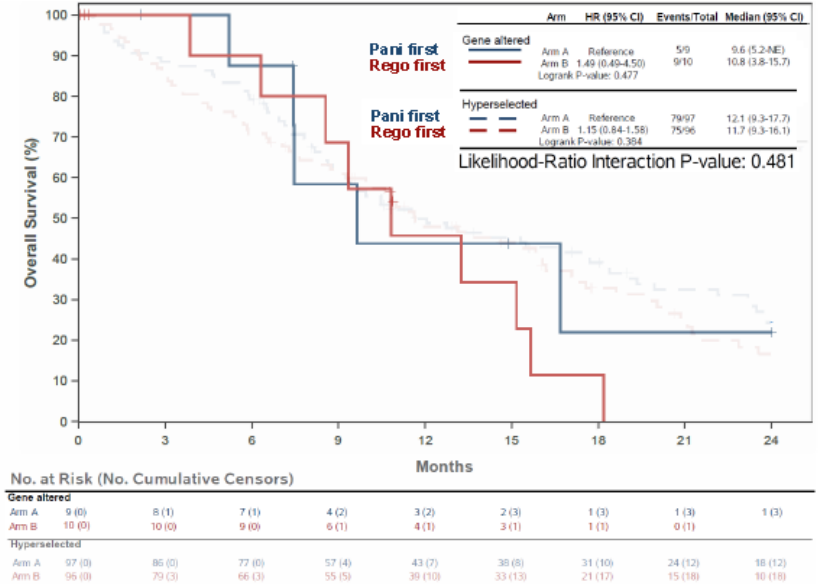
Negative: No difference in OS was detected between the two treatment sequences

# Overall survival, molecular hyperselection

## Overall survival

### Intention-to-treat population



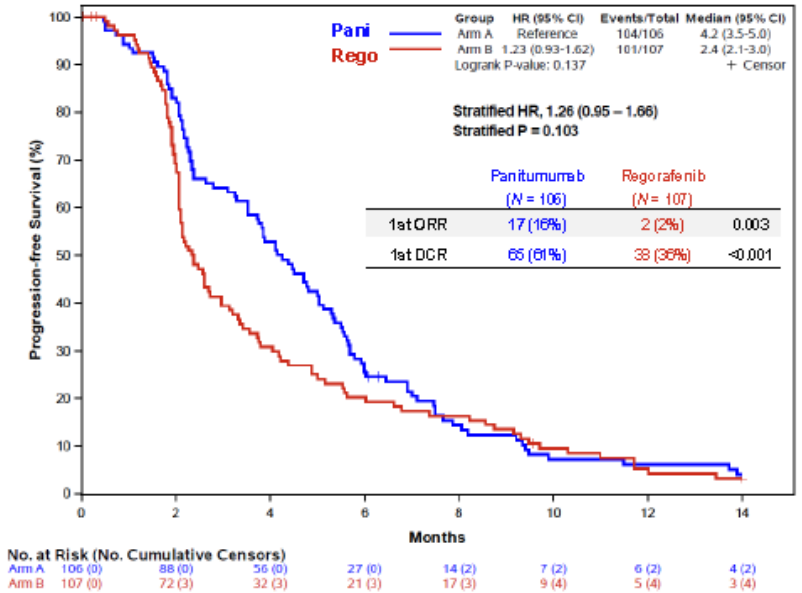

No differential OS benefit from the treatment sequence was detected according to molecular hyperselection.

**Limitations**

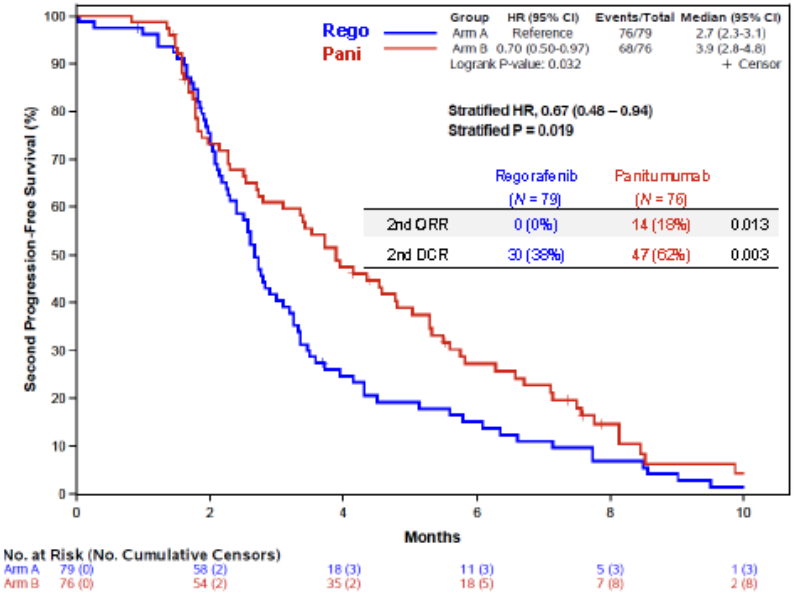
- Primary endpoint not met (OS negative)
- Phase II design, limited power
- **Cross-over and subsequent therapies confound OS**
- **Not yet integrated with FTD/TPI + Bev standard**

# Secondary endpoints: 1st and 2nd PFS, ORR and DCR

## 1st PFS - 1st ORR - 1st DCR




## 2nd PFS - 2nd ORR - 2nd DCR




**Anti-EGFR re-treatment is confirmed superior in terms of PFS, ORR, and DCR, regardless of the treatment sequence**

# Circulating Tumour (ct) DNA-Guided Anti-EGFR Rechallenge Strategy in Metastatic Colorectal Cancer (mCRC): Final results of the phase II randomized CITRIC trial

## CITRIC: Study Design

*Multicenter, ctDNA Biomarker-Enriched, Randomized, Phase II Study*

**Key eligibility criteria**

- **RAS wt, MSS mCRC**
- ECOG PS 0-1
- Previous treatment with fluoropyrimidine, oxaliplatin, irinotecan +/- anti-angiogenic drug
- Acquired resistance to 1L anti-EGFR containing regimen*
- PD to 2L anti-EGFR-free regimen

**Stratification factors:** Tumor location (left vs. right); Metastatic sites (1-2 vs.≥3)

**Molecular Screening**

**RAS, BRAF, EGFR-ECD ctDNA wt**
assessed by central molecular testing#

R 1:1

- **Rechallenge with Cetuximab 500mg/m² + Irinotecan 180mg/m², q2w**
- **Investigator's choice (IC)** (excluding anti-EGFR agents)

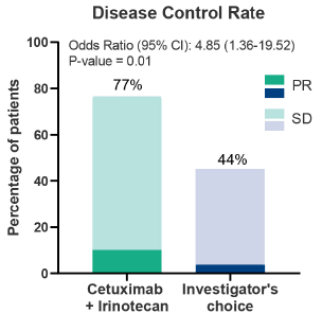
**Primary Endpoint:**
- **Overall Response Rate (ORR)** by RECIST v1.1, Investigator-assessed

**Secondary Endpoints:**
- DCR, PFS, OS, Safety

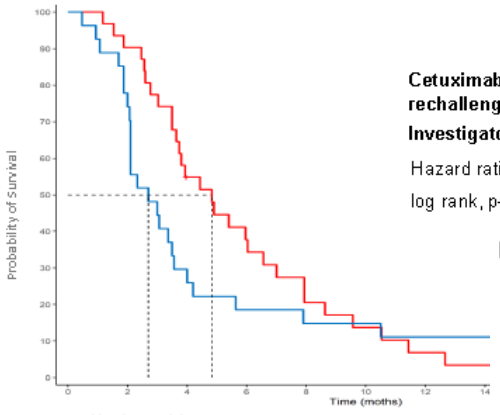
**Exploratory Endpoints:**
- Biomarker Assessment

**Primary endpoint not met**

| | Cetuximab + Irinotecan Rechallenge N=31 | Investigator's choice N=27 | p-value |
|---|---|---|---|
| **ORR (90% CI), %** | 9.7 (2.7 – 23.2) | 3.7 (0.2– 16.4) | 0.6 |
| **PR, %** | 3 (9.7) | 1 (3.7) | |
| **SD, %** | 21 (67.7) | 11 (40.7) | |
| **PD, %** | 7 (22.6) | 15 (55.6) | |
| **NE, %** | 0 (0) | 0 (0) | |
| **Disease control rate (90% CI), %** | 77.7 (61.7 – 88.9) | 44.4 (28.1 - 61.8) | 0.01 |



# Progression Free Survival in ITT




| | Number of events, n (%) |
|---|---|
| **Cetuximab + irinotecan rechallenge** | 30 (97%) |
| **Investigator's choice** | 26 (96%) |

Hazard ratio 0.6 (90% CI, 0.4-1)

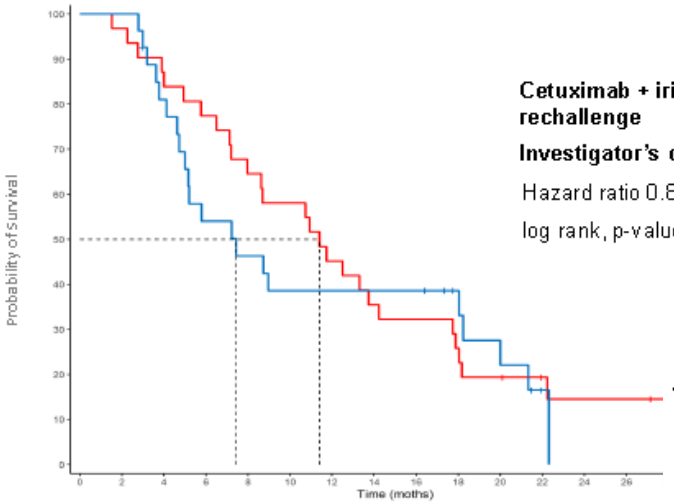
log rank, p-value = 0.1

Median Progression Free Survival, months (95% CI)

**4.64 months** (3.12 - 6.15)

**2 months** (0.96 - 3.17)

# Overall Survival in ITT




| | Number of even n (%) |
|---|---|
| **Cetuximab + irinotecan rechallenge** | 26 (84%) |
| **Investigator's choice** | 21 (78%) |

Hazard ratio 0.8 (90% CI, 0.54-1.43)

log rank, p-value = 0.6

Median Overall Survival, months (95% CI)

**11.3 months** (7.8 - 14.7)

**7.3 months** (3.7 – 10.9)

**PFS favored rechallenge across key patient subgroups, except for patients without liver involvement**

**Rechallenge with cetuximab plus irinotecan numerically increased overall survival compared to investigator's choice. There was a 75% crossover rate**

I Jornada Regional

POST-ESMO

# Zanzalintinib plus Atezolizumab vs Regorafenib in Patients with Previously Treated Metastatic Colorectal Cancer:

## Primary Overall Survival Analysis from the Randomized, Open-Label, Phase 3 STELLAR-303 Study

### Patient Population

- Aged ≥18 years
- Documented to not have MSI-H or dMMR status
- mCRC that radiographically progressed on or was refractory or intolerant to prior standard-of-care therapy, which had to include all the following (if approved and available in the country where the patient is randomized):
  - Fluoropyrimidine, irinotecan and oxaliplatin ± anti-VEGF antibody
  - Anti-EGFR antibody (if *RAS* wild type)
  - BRAF inhibitor (if known *BRAF* V600E mutation)

R 1:1
N=901

- Zanzalintinib 100 mg PO QD + Atezolizumab 1200 mg IV Q3W (n=451)*
- Regorafenib 160 mg PO QD (days 1–21 of each 28-day cycle) (n=450)*

No liver metastases 15.9 vs 12.7 m
HR 0.79 (0.61-1.03, p= 0.087

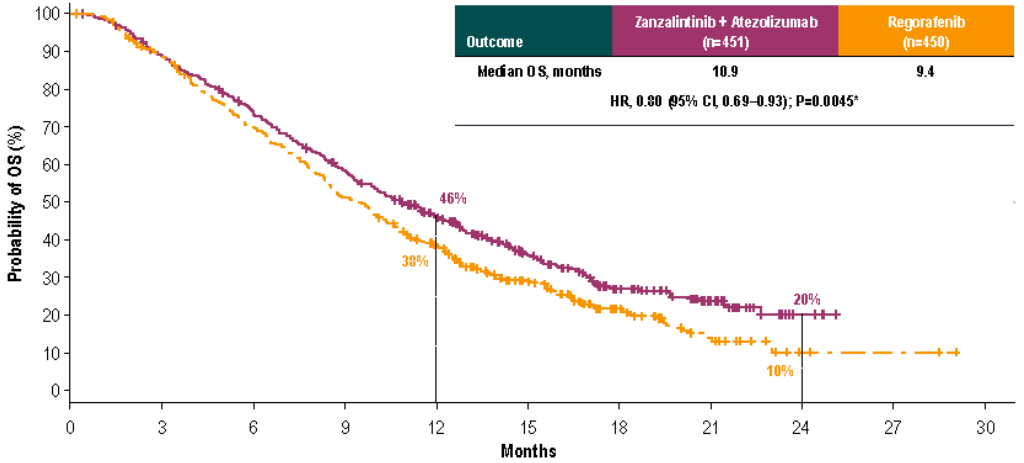
### Endpoints

| | |
|---|---|
| Dual primary | OS in the ITT population<br>OS in patients without liver metastases (nlmITT) |
| Key secondary | PFS,† ORR,† Safety‡ |

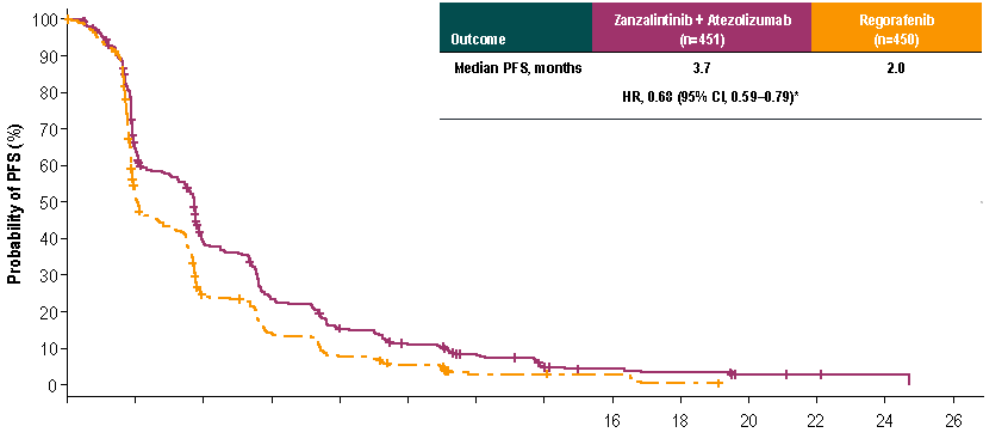
If median OS with the standard treatment is <12 months

| | |
|---|---|
| GRADE 4 | HR ≤0.65 AND gain ≥3 months |
| | Increase in 2-year survival ≥10% (if ≥20% of patients on experimental arm have reached 2-year OS) |
| GRADE 3 | HR ≤0.65 AND gain ≥2 - <3 months |
| GRADE 2 | HR ≤0.65 AND gain ≥1.5 - <2 months |
| | HR >0.65 - 0.70 AND gain ≥1.5 months |
| GRADE 1 | HR >0.70 OR gain <1.5 months |

## OS Analysis (ITT Population)



# PFS (ITT Population)



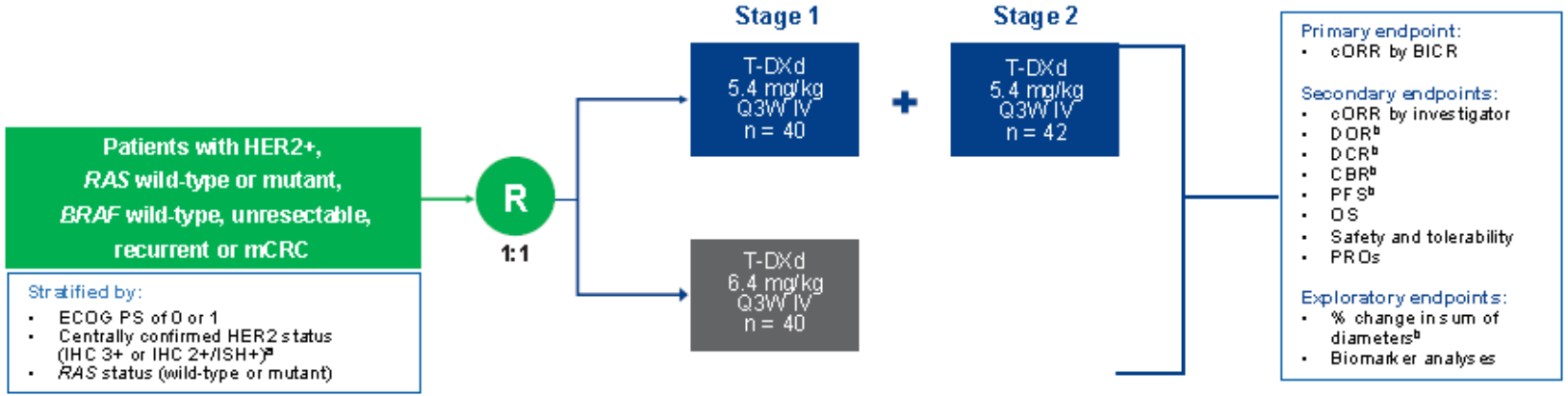

| Outcome | Zanzalintinib + Atezolizumab (n=451) | Regorafenib (n=450) |
|---|---|---|
| Median PFS, months | 3.7 | 2.0 |
| | HR, 0.68 (95% CI, 0.59–0.79)* | |

# Safety Overview (Safety Population)

| Event, n (%) | Zanzalintinib + Atezolizumab (n=446) | Regorafenib (n=434) |
|---|---|---|
| **Treatment-related adverse events** | | |
| Any-grade | 423 (95) | 399 (92) |
| Grade 3 | 248 (56) | 143 (33) |
| Grade 4 | 15 (3) | 17 (4) |
| **Serious adverse events** | 255 (57) | 184 (42) |
| **Serious treatment-related adverse events** | 118 (26) | 45 (10) |
| **Adverse events leading to discontinuation of all treatment** | 82 (18) | 64 (15) |
| **Dose modification due to an adverse event*** | | |
| Dose reduction of zanzalintinib/regorafenib | 270 (61) | 174 (40) |
| Dose delay of atezolizumab | 193 (43) | NA |

# Trastuzumab deruxtecan (T-DXd) in patients with HER2-positive (HER2+) metastatic colorectal cancer (mCRC): Final analysis of DESTINY-CRC02, a randomized, phase 2 trial

**Based in part on the results of DESTINY-CRC02, T-DXd has been approved in several countries for the treatment of patients with previously treated unresectable or metastatic HER2 IHC 3+ solid tumors, including CRC**




This study was not powered to statistically compare the 2 arms.
The site staff were blinded to treatment assignment through the roles and permissions document in the interactive response technology system.
Treatment assignments were also unknown to patients, central imaging readers, and the interstitial lung disease adjudication committee.

**Objective:** To evaluate the efficacy and safety of T-DXd 5.4 mg/kg and 6.4 mg/kg at the final analysis of DESTINY-CRC02 (DCO, December 4, 2024)

| | Primary analysis (DCO, November 1, 2022) | | Final analysis (DCO, December 4, 2024) | |
|---|---|---|---|---|
| **T-DXd dose** | **5.4 mg/kg n = 82** | **6.4 mg/kg n = 40** | **5.4 mg/kg n = 82** | **6.4 mg/kg n = 40** |
| **Treatment duration, median (range), mo** | 5.5 (0.7-13.2) | 4.9 (0.7-13.8) | 5.5 (0.7-34.3)[a] | 4.9 (0.7-29.2)[a] |
| **Follow-up, median (range), mo** | 8.9 (0.5-17.1) | 10.3 (0.7-16.4) | 14.2 (0.5-34.0) | 12.7 (0.7-36.6) |
| **cORR (95% CI), %** | 37.8 (27.3-49.2) | 27.5 (14.6-43.9) | 37.8 (27.3-49.2) | 27.5 (14.6-43.9) |
| **DOR, median (95% CI), mo** | 5.5 (4.2-8.1) | 5.5 (3.7-NE) | 5.5 (4.2-8.1) | 5.5 (3.7-9.8) |
| **PFS, median (95% CI), mo** | 5.8 (4.6-7.0) | 5.5 (4.2-7.0) | 5.8 (4.6-7.0) | 5.5 (4.2-7.0) |
| **OS, median (95% CI), mo** | 13.4 (12.5-16.8) | NE (9.9-NE) | 15.9 (12.6-18.8) | 19.7 (9.9-25.8) |
| **Drug-related grade ≥3 TEAE, %[a]** | 41.0 | 48.7 | 42.2 | 48.7 |
| **Adjudicated drug-related ILD, %[a]** | 8.4 (1 grade 1; 6 grade 2) | 12.8 (2 grade 1; 2 grade 2; 1 grade 5[b]) | 9.6 (2 grade 1; 6 grade 2) | 17.9 (2 grade 1; 4 grade 2; 1 grade 5[b]) |

**OS consistent in key subgroups**

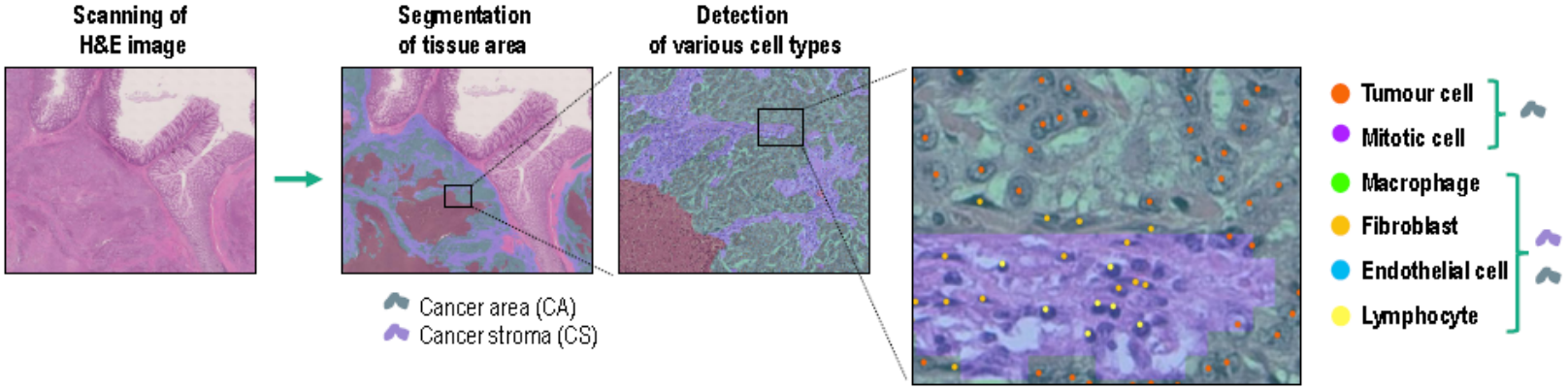
- Prior antiHER2 treatment.- 15.9 vs 14.2 m ----19.7 vs 15.7 m
- HER2 score status (3+/2+ ISH +).- 18.6 vs 6.8 m------22.7 vs NA
- RAS status (WT /Mutant).- 16.7 vs 14.9 m ---------19.7 vs NA

**These findings support T-DXd 5.4 mg/kg as the optimal single-agent dose for patients with previously treated HER2+ mCRC, irrespective of *RAS* mutations and prior anti-HER2 therapy.**

# Leveraging Artificial Intelligence to predict immune checkpoint inhibitor (ICI) efficacy in proficient MMR mCRC: Translational analyses of AtezoTRIBE and AVETRIC trials

## Exploring AI platform

Lunit SCOPE IO is an AI-powered whole-slide images (WSIs) analyzer of different infiltrating cell populations in the TME.

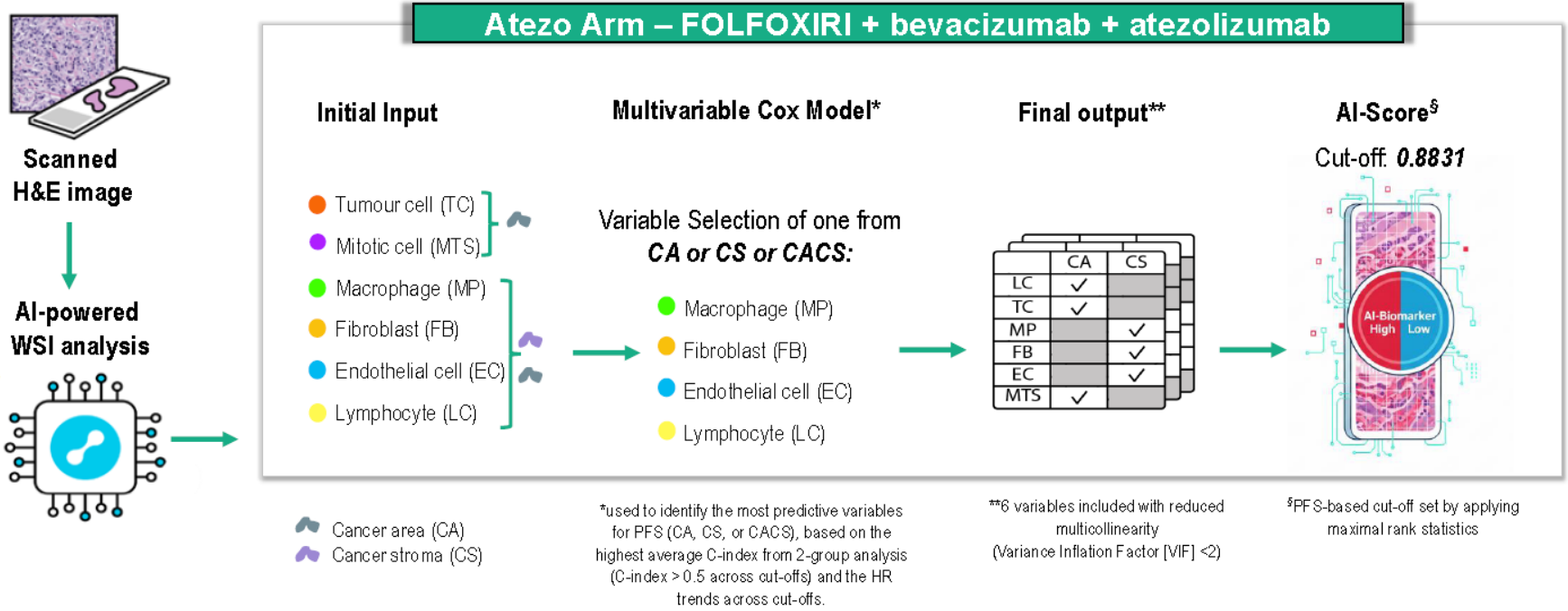



Cell densities measured included:

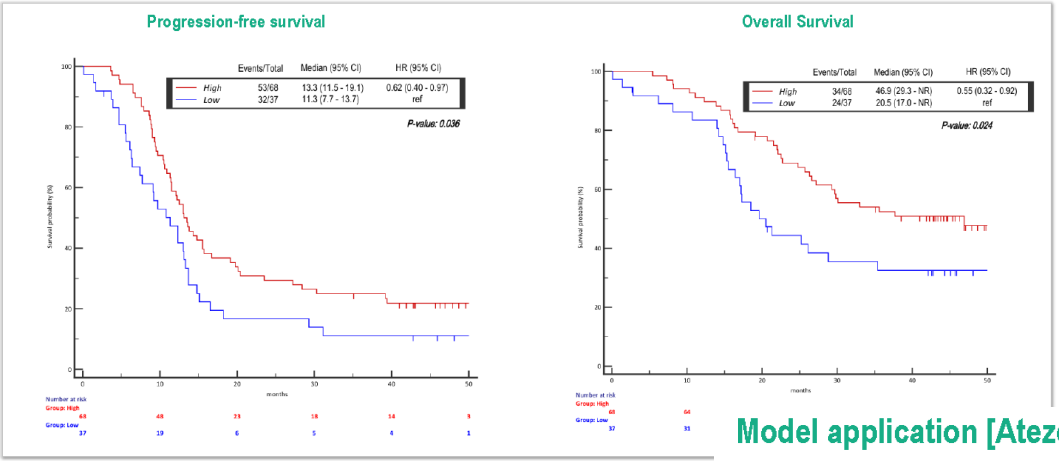
- ✓ Tumour cells (TC) and mitotic cells (MTS) within the CA
- ✓ Lymphocytes (LC), macrophages (MP), fibroblasts (FB), and endothelial cells (EC) across both CA and CS

# Leveraging Artificial Intelligence to predict immune checkpoint inhibitor (ICI) efficacy in proficient MMR mCRC: Translational analyses of AtezoTRIBE and AVETRIC trials

## Model development



# Model application [AtezoTRIBE] - Outcomes according to AI-biomarker - Atezo arm

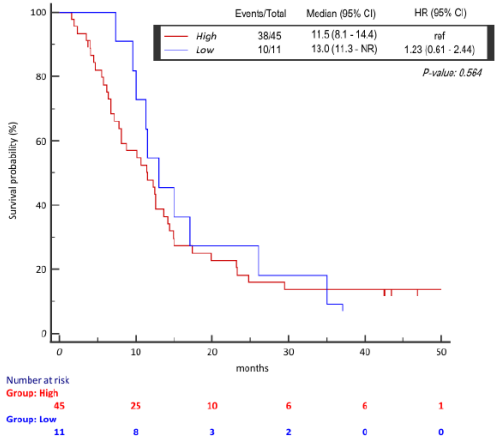


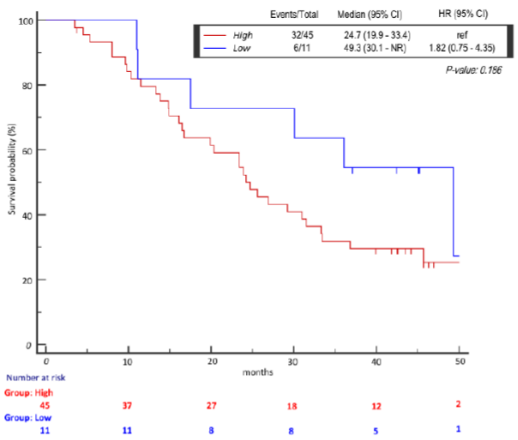




**AI-derived spatial biomarker predicts ICI benefit in pMMR mCRC.**

# Model application [AtezoTRIBE] - Outcomes according to AI-biomarker - Control arm



# Others

- Nakamura Y et al. #734MO.- A blood-based screening test for early detection of CRC
- Osterlund E et al. #732MO.- INTERCEPT study: ctDNA prognostic in CRC
- Mascaró-Baselga P et al #728MO.- Beyond ctDNA “mutation negative” approach, relative MAF may help refine patient selection for antiEGFR rechallenge and warrants further investigation
- Kopetz S et al. #729MO.- BREAKWATER: More pts in the EC+mFOLFOX6 arm had undetectable BRAF VAF at C2D15 vs control and undetectable $BRAF_{V600E}$ ctDNA at C2D15 correlates with longer OS
- Booth CM et al. #LBA28.- Predictors of adherence to the SEP and PA – CHALLENGE trial
- Cecchini M et al.#731MO.- Telisotuzumab adizutecán + BVZ (phase I) had a manageable safety and promising efficacy compared to SOC in 3L-and-beyond patients with CRC
- #727MO.- OPTIPRIME: stop-and-go FOLFOX + PNT achieves 25 months disease control
- #730MO.- TRICOMB.-: 55% ORR – statistically positive phase II in frail mCRC
- #LBA34.- DEFIANCE: Negative overall but significant PFS and OS benefit in DKK1-high MSS mCRC first biomarker-driven IO signaling in this setting

# CANCER COLORRECTAL - CONCLUSIONES

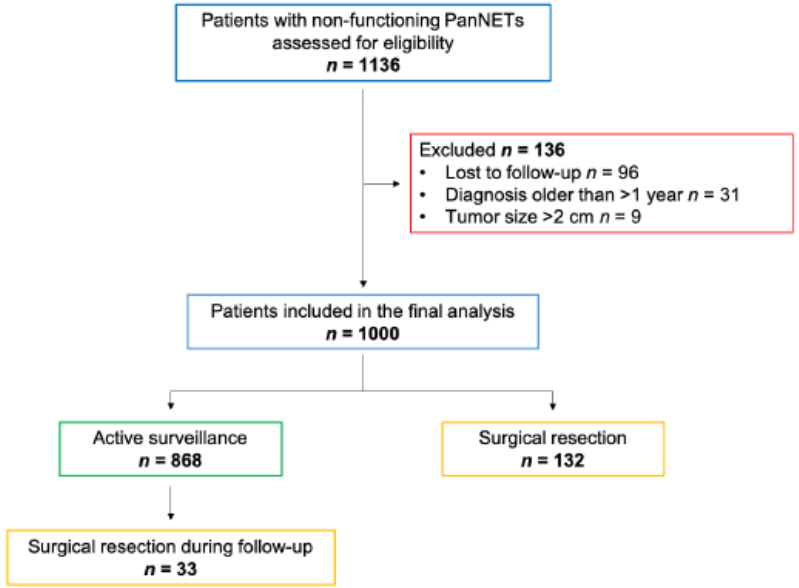
- Preparados para usar ctDNA para selección pacientes en enfermedad localizada?
- Inmunoterapia.- Tratamiento Neoadyuvante enfermedad localizada MSI-H
- Doblete IT – tratamiento estándar en enfermedad avanzada
- Rechallenge AntiEGFR – datos controvertidos – posicionamiento tras TAS + BVZ
- Trastuzumab Deruxtecan – Dosis 5,4 mg/Kg – Pendiente aprobación

# TUMORES NEUROENDOCRINOS

# Management of Asymptomatic Sporadic Nonfunctioning Pancreatic Neuroendocrine Neoplasms ≤2 cm: A Prospective International Observational Multicentric Cohort Study

ASPEN Study

## Study population




87% ACTIVE SURVEILLANCE (*n* = 868)

SURGERY DURING FOLLOW-UP (*n* = 33) 4%

13% SURGERY AT DIAGNOSIS (*n* = 132)

# Active surveillance vs. surgical resection

| Variable | Overall n 1000 (%) | Active surveillance n 868 (%) | Surgical resection n 132 (%) | p |
|---|---|---|---|---|
| Gender, male | 549 (55) | 479 (55) | 70 (53) | 0.643 |
| Age, years* | 64 (55-71) | 65 (56-72) | 59 (50-68) | <0.001 |
| BMI, kg/m² | 24.5 (23.6-29.6) | 23.7 (21.2-26.6) | 23.3 (20.9-25.7) | 0.049 |
| Diabetes | 176 (18) | 153 (18) | 23 (17) | 0.890 |
| EGOG PS score, ≥2 | 20 (2) | 20 (2) | 0 (0) | 0.095 |
| Year of diagnosis | | | | <0.001 |
| 2017-2020 | 587 (59) | 485 (56) | 102 (77) | |
| 2021-2024 | 413 (41) | 383 (44) | 30 (23) | |
| Tumor site, body/tail | 651 (65) | 556 (64) | 95 (72) | 0.076 |
| Radiological tumor size, mm* | 13 (10-15) | 12 (10-15) | 16 (13-19) | <0.001 |
| MPD diameter, mm* | 2.0 (1.0-2.7) | 2.0 (1.0-2.0) | 3.0 (2.0-5.0) | <0.001 |
| rN status, N1 | 2 (0.2) | 0 (0) | 2 (2) | 0.017 |
| rM status, M1 | 6 (0.6) | 0 (0) | 6 (5) | <0.001 |
| $^{18}$F-FDG PET | | | | 0.090 |
| Not performed | 884 (88) | 765 (88) | 119 (90) | |
| Negative | 76 (8) | 71 (8) | 5 (4) | |
| Positive | 40 (4) | 32 (4) | 8 (6) | |
| Tumor grade | | | | 0.012 |
| G1 | 336 (34) | 306 (35) | 30 (23) | |
| G2 | 52 (5) | 42 (5) | 10 (8) | |
| Not evaluable | 612 (61) | 520 (60) | 92 (70) | |

*Reported as median (interquartile range)

| Variable | n (%) |
|---|---|
| **Tumor size**, mm* | 15 (10-17) |
| **pT status**, T2 | 13 (10) |
| **Tumor grade** | |
| G1 | 92 (72) |
| G2 | 34 (27) |
| G3 | 1 (1) |
| **Ki67**, %* | 2 (1-2.9) |

- MPD diameter, tumor grade, tumor size
- Age and BMI
- Nodal metastases
- Liver metastases

| Variable | n (%) |
|---|---|
| **pN status**, N1 | 8 (6) |
| **M status**, M1 | 4 (3) |
| **Aggressive feature(s)** | 27 (21) |

*At least 1 of the following: pN1, M1, Ki67 >5%, perineural and microvascular invasion

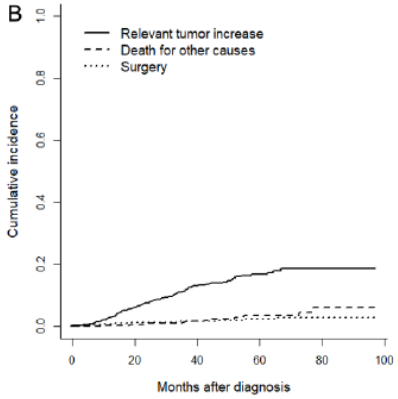
*n* = 24/27 radiological tumor size >10 mm
*n* = 2/27 MPD dilation

| Patient | Gender, age | Rad tumor size | Preop G | Ki67 | MPD dilation |
|---|---|---|---|---|---|
| #1 | F, 51 | 20 mm | NA | NA | No |
| #2 | F, 76 | 19 mm | 2 | 6% | No |
| #3 | F, 70 | 7 mm | 2 | 4% | Yes |
| #4 | F, 58 | 20 mm | 2 | 10% | No |

*Patients #5 and #6 liver lesions defined as benign after surgery

# Relevant tumor growth during follow-up

*n* = 8



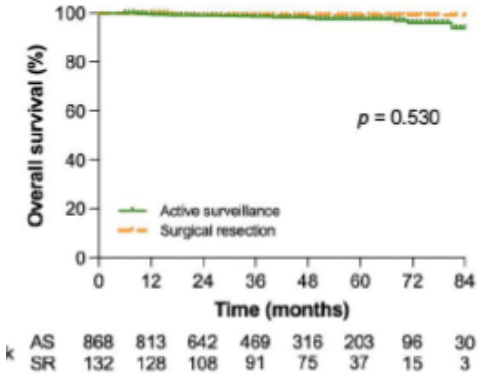

| Time | Cumulative incidence |
|---|---|
| 2 years | **7.5%** (95%CI 5.8%-9.5%) |
| 5 years | **16.7%** (95%CI 13.6%-20.1%) |
| 7 years | **18.5%** (95%CI 14.9%-22.4%) |

**Smaller tumor size at diagnosis**

was the only independent determinant of relevant tumor growth during follow-up

- *Tumor size <1 cm*: HR 1.69, 95%CI 1.11-2.56, *p*=0.014

Only n=1 reached a final tumor size >2 cm




*n* = 33

## Surgery during follow-up

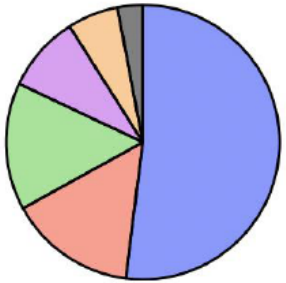
| Time | Cumulative incidence |
|---|---|
| 2 years | **2.2%** (95%CI 1.4%-3.4%) |
| 5 years | **5.3%** (95%CI 3.4%-7.7%) |
| 7 years | **18.5%** (95%CI 5.1%-12.6%) |

***Predictors of surgery during follow-up***

**Larger tumor size at diagnosis**

*Tumor size*: HR 1.23, 95%CI 1.11-1.36, *p*<0.001

*Tumor size ≥ 1.5 cm*: HR 4.11, 95%CI 2.04-8.28, p<0.001

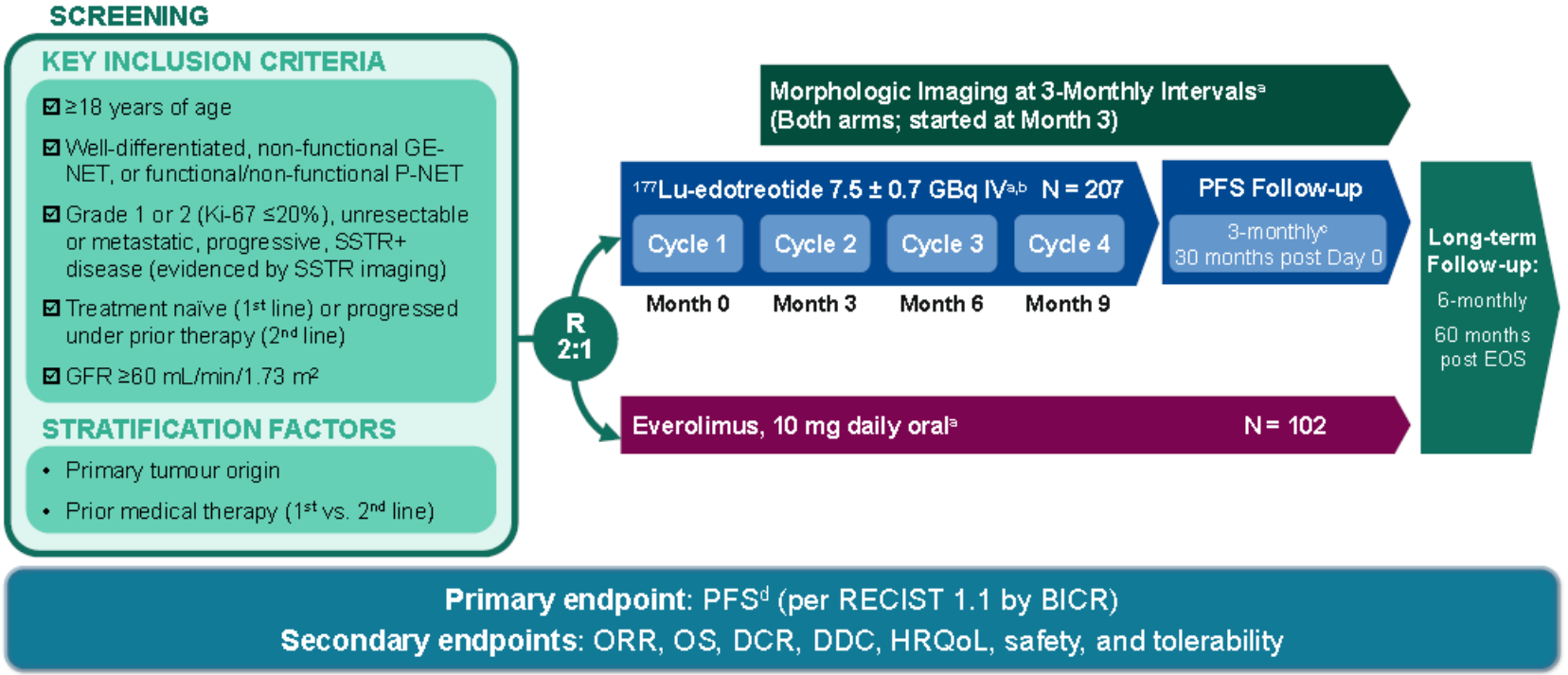


- Tumor size increase (n 17, 52%)
- Patient preference (n 5, 15%)
- Physician preference (n 5, 15%)
- Increased MPD dilation (n 3, 9%)
- Appearance of metastatic disease (n 2, 6%)
- Onset of symptoms (n 1, 3%)

*n* = 3 patients developed liver metastase (*n*=2 underwent surgery)

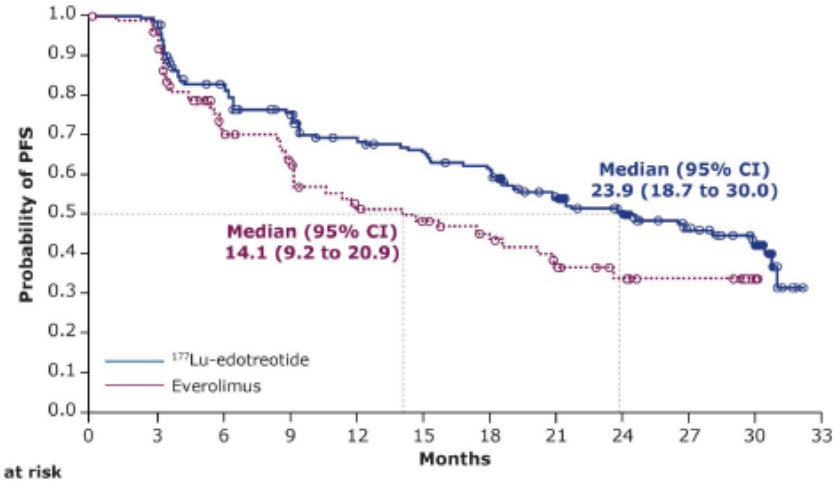
# Efficacy, safety and subgroup analysis of $^{177}$Lu-edotreotide vs everolimus in patients with grade 1 or grade 2 GEP-NETs: Phase 3 COMPETE trial

Prospective, randomised, controlled, open-label, multi-centre phase 3 trial



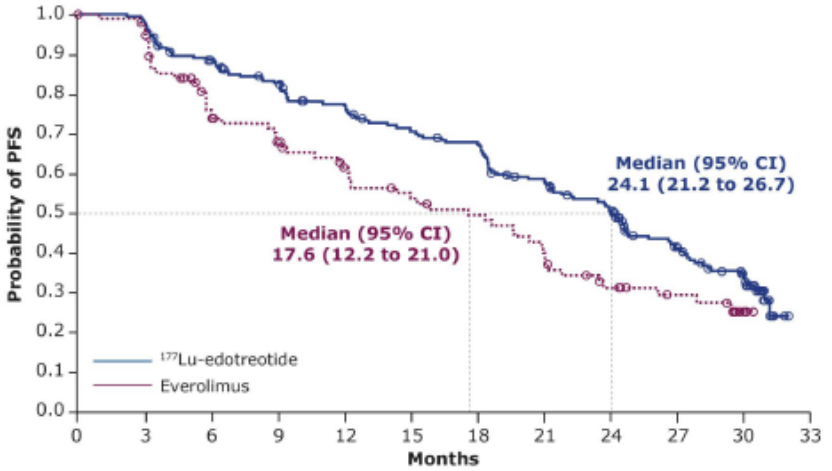
# POST-ESMO

## Central Assessment (BICR)




| Patients at risk | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $^{177}$Lu-edotreotide | 207 | 195 | 157 | 138 | 120 | 112 | 104 | 83 | 68 | 51 | 31 | 0 |
| Everolimus | 102 | 91 | 58 | 48 | 36 | 32 | 27 | 20 | 14 | 11 | 2 | 0 |

## Local Assessment




| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 207 | 197 | 174 | 159 | 145 | 130 | 123 | 103 | 87 | 60 | 36 | 0 |
| | 102 | 93 | 66 | 57 | 47 | 40 | 36 | 28 | 20 | 15 | 4 | 0 |

mPFS was **significantly longer** in the $^{177}$Lu-edotreotide arm vs the everolimus arm:

- **Central assessment**: **23.9** vs. **14.1** months; p=0.022; HR 0.67, 95% CI [0.48, 0.95]
- **Local assessment**: **24.1** vs. **17.6** months; p=0.010; HR 0.66; 95% CI [0.48, 0.91]

| | 177-Lu edotreotide | Everolimus | |
|---|---|---|---|
| **GE-NET** | 23.9 m | 12.0 m | HR 0.64 p 0.090 |
| **P-NET** | 24.5 m | 14.7 m | HR 0.70 p 0.114 |

| | 177-Lu edotreotide | Everolimus | |
|---|---|---|---|
| **G1** | 30.0 m | 23.7 m | HR 0.89 p 0.753 |
| **G2** | 21.7 m | 9.2 m | **HR 0.55 p 0.003** |

| | 177-Lu edotreotide | Everolimus | |
|---|---|---|---|
| **1st line** | NR | 18.1 m | HR 0.604 p 0.249 |
| **2nd line** | 23.9 m | 14.1 m | **HR 0.68 p 0.039** |

By both **central and local assessment**, ORR was **significantly higher** in the $^{177}$Lu-edotreotide arm:

- **Central assessment**: **21.9%** vs. **4.2%**; p<0.0001
- **Local assessment**: **30.5%** vs. **8.4%**; p<0.0001

# Efficacy and Safety of Targeted Alpha Therapy $^{212}$Pb-DOTAMTATE in Patients With Unresectable or Metastatic Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs) Previously Treated with Peptide Receptor Radionuclide Therapy (PRRT): Results of a Phase 2 Study

## INCLUSION CRITERIA

- Adults ≥18 years of age
- Histologically confirmed unresectable or metastatic NETs
- Somatostatin receptor-positive (SSTR+) imaging
- At least 1 site of measurable disease per RECIST 1.1
- Patients previously exposed to RLT in Cohort 2 who had progressive disease after receiving ≤4 doses of $^{177}$Lu-SSA and received their last dose ≥6 months prior to Day 1

## TREATMENT ARMS

**Cohort 1**
RLT-naïve
GEP-NETs
N = 35

**Cohort 2**
**RLT-exposed**
**GEP-NETs**
**N = 26**

**$^{212}$Pb-DOTAMTATE**
67.6 µCi/kg every 8 weeks
up to 4 doses

## STUDY ENDPOINTS

**Primary endpoints:**

- Overall response rate (ORR) as per investigator's assessment[a,b]
- Incidence of adverse events (AEs)

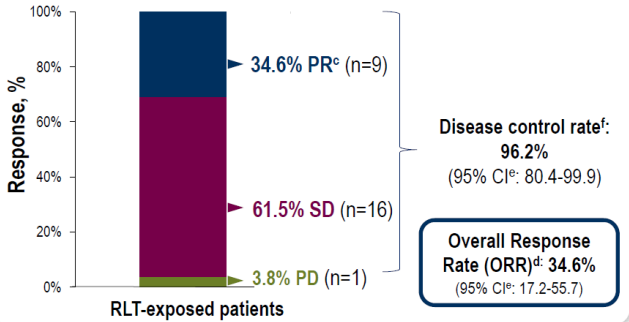
**Key secondary endpoints:**

- Progression free survival (PFS)[b]
- Time to tumor progression (TTP)[b]
- Overall survival (OS)
- Health-related Quality of Life (HRQoL)

**Cohort 2 of the ALPHAMEDIX02 Phase 2, open-label, multicenter study evaluated the efficacy and safety of $^{212}$Pb-DOTAMTATE in patients with unresectable or metastatic GEP-NETs previously exposed to RLT**

# Primary Endpoint ORR and DoR in RLT-Exposed Patients[a,b]

## OBJECTIVE RESPONSE RATE
(N=26)




Disease control rate[f]: 96.2%
(95% CI[e]: 80.4-99.9)

Overall Response Rate (ORR)[d]: 34.6%
(95% CI[e]: 17.2-55.7)

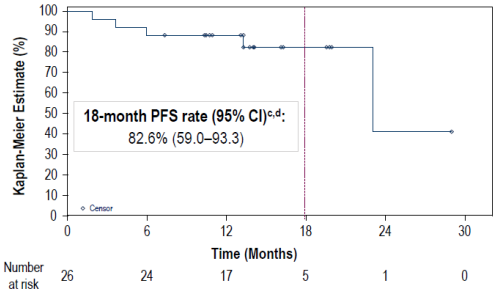
| Duration of Response (DoR) per KM Estimate[g], % | N=9[h] |
|---|---|
| ≥ 18 months (n=1) | 100 (95% CI: 100-100) |

84.6% of patients received all 4 doses of $^{212}$Pb-DOTAMTATE

- Per the BICR analyses, there was a clinically meaningful ORR of 19.2%[i] and a disease control rate of 100% in RLT-exposed patients
- 100% of patients with a PR experienced durable responses maintained over ≥18 months

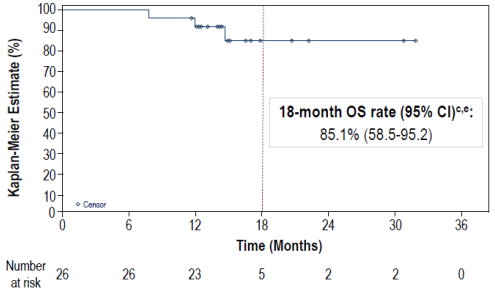
**The primary endpoint was met, where a clinically meaningful ORR of 34.6% and a high disease control rate of 96.2% was achieved in RLT-exposed patients. 100% of patients with a PR experienced durable responses maintained over ≥18 months**

## PROGRESSION-FREE SURVIVAL (PFS)




**An 18-month PFS rate (95% CI)** of **88.0% (67.3–96.0)** was observed in the BICR analyses

## OVERALL SURVIVAL (OS)



# Others

- Capdevila et al.- Belzutifan in pretreated pNETs.- Phase II trial
- Del Olmo-Garcia.- A prediction tool for malnutrition and sarcopenia in GEP TNE (NUTRIGETNE)
- Zhao et al.- Alveltamig (ZG006) Trispecific T-Cell engager targeting DLL3/DLL·/CD3 in refractory NEC
- Strosberg et al.- ALPHAMEDIX 02 Trial.- PRRT naive treated with targeted alpha therapy 212Pb-DOTAMTATE
- Chauhan et al. – ETCTN 10388.- Phase I triapine in combination with 177Lu-DOTATATE in WD-GEP NETs
- Halfdanarson et al.- 212Pb –VMT-α-NET targeted alpha-partycle therapy in advanced SSTR2 NETs
- Jimenez et al.- LITESPARK 015.- Belzutifan in advanced phemochromocytoma and paraganglyoma
- Ye et al.- ZG005 in combination with etoposide and cisplatin for the first-line treatment of advanced neuroendocrine carcinoma

# TUMORES NEUROENDOCRINOS - CONCLUSIONES

- Vigilancia activa tratamiento adecuado para NF-pNETs ≤ 2 cms
- $^{177}$Lu-edotreotide > Everolimus (2ª línea/G2) – Posicionamiento en guías
- Emisores alfa ($^{212}$Pb) – Eficacia pacientes pretratados con PRRT (también en 1ª línea)