
GI
connect
POWERED BY COR2ED

MEETING SUMMARY
ASCO 2019, Chicago, USA

Dr. Victor Hugo Fonseca
A.C. Camargo Cancer Center, Sao Paulo, Brazil

HIGHLIGHTS ON GI CANCER

DISCLAIMER

Please note: The views expressed within this presentation are the personal opinions of the author. They do not necessarily represent the views of the author's academic institution or the rest of the GI CONNECT group.

This content is supported by an Independent Educational Grant from Bayer.

FOxTROT: AN INTERNATIONAL RANDOMISED CONTROLLED TRIAL IN 1052 PATIENTS EVALUATING NEOADJUVANT CHEMOTHERAPY FOR COLON CANCER

Seymour M, et al. ASCO 2019, Abst #3504

FOxTROT STUDY

GI connect
POWERED BY COR2ED

Background

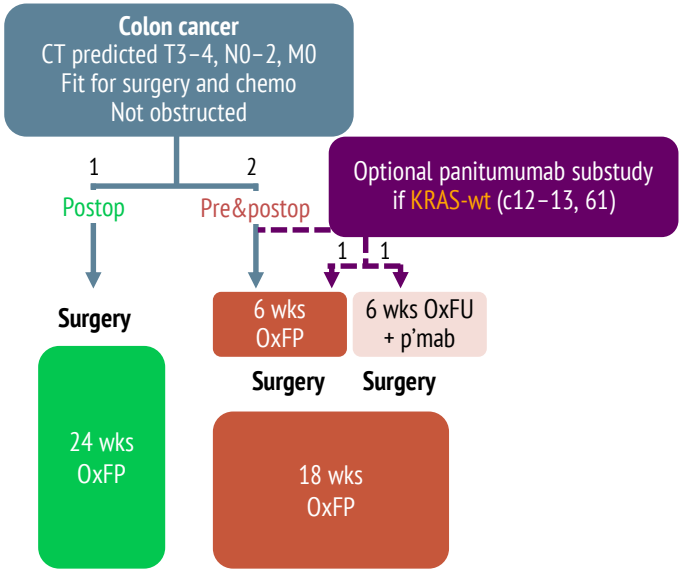
- Neoadjuvant treatment is standard in many non-metastatic GI malignancies, including rectal cancer
- Neoadjuvant treatment in colon cancer presents putative benefits:
  - Early treatment of micro-metastatic disease
  - Reduction in incomplete resection rates
  - Increased tolerability (compared to adjuvant treatment)
  - Opportunity to tailor post-operative treatment based on pathological response
- Nonetheless, there are potential drawbacks of the neoadjuvant approach:
  - Concerns regarding tumour growth and increased need for urgent surgery
  - Potential overtreatment of patients with low-risk disease due to inaccurate radiological staging

GI, gastrointestinal

FOxTROT Collaborative Group. Lancet Oncol 2012;13(11):1152-60.

FOxTROT STUDY

STUDY DESIGN



Primary outcome

- Relapse/persistent disease up to 2 yrs

Secondary outcomes

- Complete resection; perioperative safety; downstaging; tumour regression

POPULATION/TREATMENT CHARACTERISTICS

Feature	Total N=1052 (%)	Pre&Postop N=698 (%)	Postop N=354 (%)
Population characteristics			
Median age (yrs)	65		
Male	64		
Left-sided tumours	51		
Radiological staging ($T4/T3_{\geqslant 5mm}$:$T3_{<5mm}$)	75:25		
Treatment characteristics			
FOLFOX		72	72
Planned treatment duration = 6 months		94	94

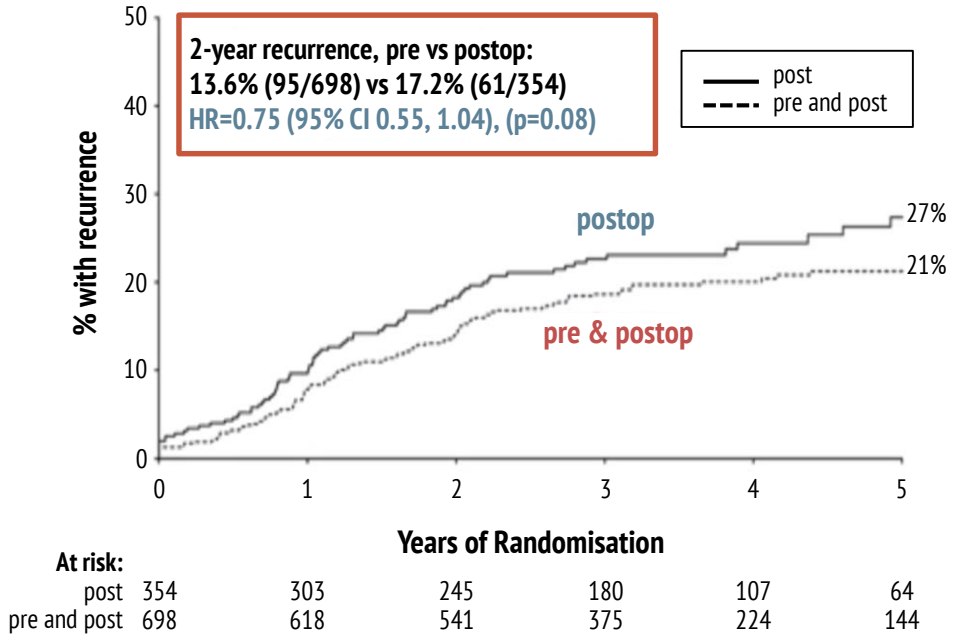
CT, computed tomography; wks, weeks; yrs, years

Seymour M, et al. J Clin Oncol 2019;37(suppl; abstr 3504).

FOxTROT STUDY

GI connect
POWERED BY COR2ED

PRIMARY OUTCOME
2-YEAR RECURRENCE PROBABILITY



Secondary outcomes	Pre&Postop N=698 (%)	Postop N=354 (%)	p
Postoperative complication			
Intra-abdominal leak/abscess	4.7	7.4	0.07
Need for further surgery	4.3	7.1	0.05
Completeness of resection			
R0 resection	93.1	88.4	0.001
T Downstaging			
pT0	4.1	0.0	< 0.0001
pT1/2	11.7	5.8	
pT3	63.7	64.5	
pT4	20.5	29.8	
N Downstaging			
pN0	59.4	48.8	< 0.0001
pN1	25.4	25.1	
pN2	15.2	25.9	
Tumor Regression Grade (TRG)			
TRG4	3.5	0.0	< 0.0001
TRG3	4.1	0.0	
TRG2	12.3	0.0	
TRG1	43.9	16.7	
TRG0	33.9	78.8	

CI, confidence interval; HR, hazard ratio

Seymour M, et al. J Clin Oncol 2019;37(suppl; abstr 3504).

FOxTROT STUDY

GI connect
POWERED BY COR2ED

Translation into clinical practice

- Preoperative chemotherapy is feasible in colon cancer
  - It might even decrease the incidence of some post-operative complications
- It also seems to improve completeness of resection and is associated with significant tumour downstaging and regression
- Nonetheless, concerns regarding patient overtreatment still remain
  - Stage I: 4%, Stage II: 45% (20% of those without strict indication to undergo chemotherapy)
- Despite a trend toward improved 2-year recurrence rate (p=0.08), these data are not conclusive and long-term survival data are needed
- Moreover, the role of neoadjuvant chemotherapy in patients with defined molecular subtypes of colon cancer (such as MSI-H tumours) deserves further clarification

MSI-H, microsatellite instability-high

Seymour M, et al. J Clin Oncol 2019;37(suppl; abstr 3504).

OLAPARIB AS MAINTENANCE TREATMENT FOLLOWING 1ST-LINE PLATINUM-BASED CHEMOTHERAPY IN PATIENTS WITH A GERMLINE BRCA MUTATION AND mPC: PHASE III POLO TRIAL

Kindler HR, et al. ASCO 2019, Abst #LBA4

POLO STUDY

GI connect
POWERED BY COR2ED

Background

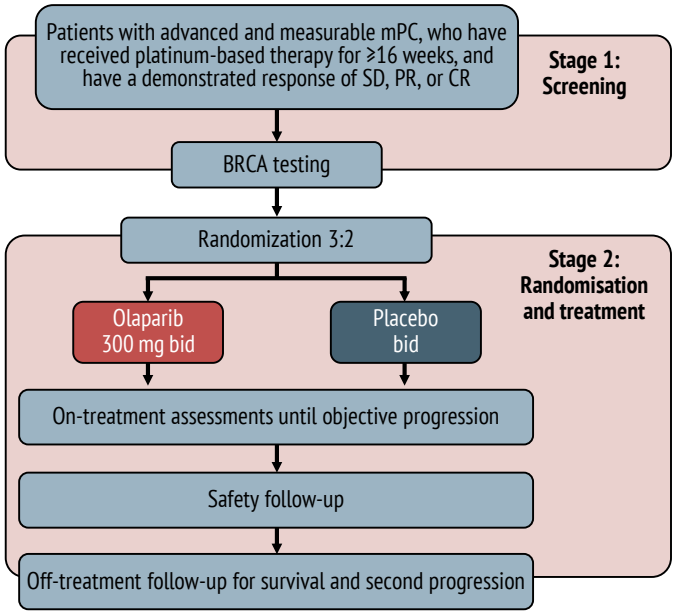
- Despite the recent advances in the management of advanced pancreatic cancer obtained with FOLFIRINOX and Gemcitabine + NAB-paclitaxel, patients' prognosis remains poor
- The study of molecular mechanisms underpinning the development of pancreatic cancer has recently pointed to promising targets in selected groups of patients
  - Anti-PD-1/PD-L1 monoclonal antibodies in microsatellite instability-high (MSI-H) tumours (<1%)
  - NTRK inhibitors in NTRK-fusion positive pancreatic cancer tumours (<1%)
  - PARP inhibitors in patients with germline BRCA-1/-2 mutations tumours (<10%)
- PARP inhibitors prevent DNA single-strand breaks from being repaired and promote DNA double-strand break
  - Catastrophic events for cells with homologous recombination DNA repair deficiency (synthetic lethality)
- So far, encouraging data for PARP inhibitors in pre-treated pancreatic cancer patients with germline BRCA (gBRCA) mutations have been shown
  - Response rate: up to 21.7%; progression-free survival: up to 4.6 months

Kaufmann B, et al. J Clin Oncol 2015;33:244-50; O'Kane GM, et al. J Clin Oncol 2019;37(suppl 4; abstr 188); Pishvaian MJ, et al. J Clin Oncol 2018;(suppl 4; abstr 521); Le D, et al. J Clin Oncol 2016;34(suppl 4; abstr 195); Lowery M, et al. Clin Cancer Res 2017;23(20):6094-100.

NAB: Nanopaticle Albumine-Bound

POLO STUDY

STUDY DESIGN



Primary outcome

- Progression-free survival (PFS)

Secondary outcomes

- Overall survival (OS); PFS2; time to subsequent treatment or death (TTST1 and TTST2); time to study treatment discontinuation or death (TDT); overall response rate (ORR); disease control rate (DCR); health-related quality-of-life (HRQoL)

POPULATION/TREATMENT CHARACTERISTICS

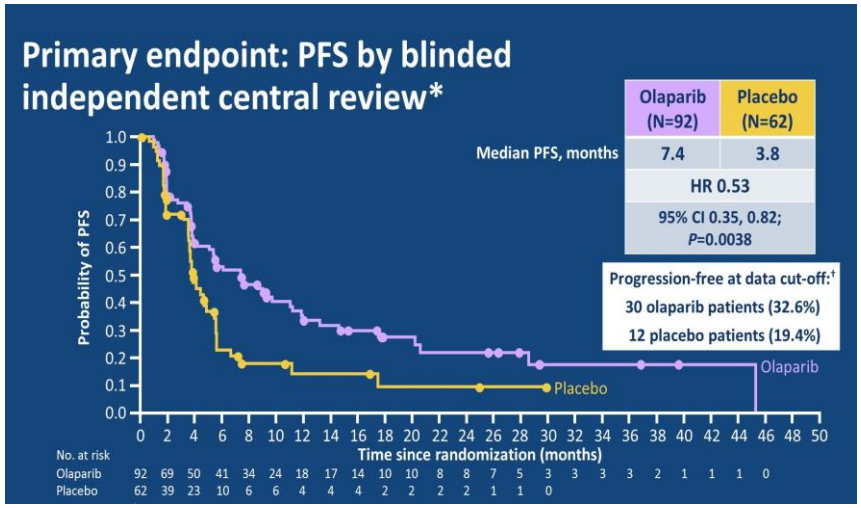
Feature	Olaparib N=92 (%)	Placebo N=62 (%)
Population characteristics		
Median age (yrs)	57 (37-84)	57 (36-75)
Male	53 (57.6)	31 (50.0)
ECOG 0	65 (70.7)	38 (61.3)
BRCA-2 mutation	62 (67.4)	46 (74.2)
First-line treatment characteristics		
FOLFIRINOX	79 (85.9)	50 (80.6)
Complete/partial response	46 (50.0)	30 (48.4)
Median duration of treatment (months)	5.0 (2.5-35.2)	5.1 (3.4-20.4)

CR, complete response; ECOG, Eastern Cooperative Oncology Group; PR, partial response; SD, stable disease

Golan T, et al. J Clin Oncol 2016;34(suppl; abstr TPS 4152); Kindler HR, et al. J Clin Oncol 2019;37(suppl; abstr LBA4)

POLO STUDY

PRIMARY OUTCOME



SECONDARY OUTCOMES

Outcome	Olaparib N=92 (%)	Placebo N=62 (%)	p
Overall survival (months)	18.9	18.1	0.68
Progression-free survival 2 - PFS2 (months)	13.2	9.2	0.26
Overall response rate (%)*	23.1	11.5	–
Duration of response (months)*	24.9	3.7	–

* In a subset of patients with measurable disease (N=78 for Ola and 52 for PBO).

2-year PFS rate

- Olaparib: 22%
- Placebo: 10%

- No significant differences in patient-reported quality-of-life outcomes
- Manageable toxicity profile (Grade 3-5 toxicity: 39.6 vs 23.3%)

CI, confidence interval; HR, hazard ratio; PFS, progression-free survival

Kindler HR, et al. J Clin Oncol 2019;37(suppl; abstr LBA4)

POLO STUDY

GI connect
POWERED BY COR2ED

Translation into clinical practice

- Patients with advanced pancreatic cancer and germline BRCA (gBRCA) mutations derive benefit from maintenance olaparib after platinum-based chemotherapy
- Germline BRCA mutation screening at the start of first-line treatment should become standard
- Nonetheless, the frequency of gBRCA mutations in pancreatic cancer patients is low and the cost-effectiveness of this strategy is currently unknown
- Also, the lack of a maintenance arm after 16 weeks of chemotherapy is not standard in advanced pancreatic cancer (PRODIGE 35)
- Furthermore, although the data are preliminary, so far no benefit in terms of overall survival has been shown (despite a low crossover rate)

Kindler HR, et al. J Clin Oncol 2019;37(suppl; abstr LBA4).

REGORAFENIB PLUS NIVOLUMAB IN PATIENTS WITH ADVANCED GC OR CRC: AN OPEN-LABEL, DOSE-FINDING, AND DOSE-EXPANSION PHASE IB TRIAL (REGONIVO, EPOC 1603)

Fukuoka S, et al. ASCO 2019, Abst #2522

REGONIVO STUDY

GI connect
POWERED BY COR2ED

Background

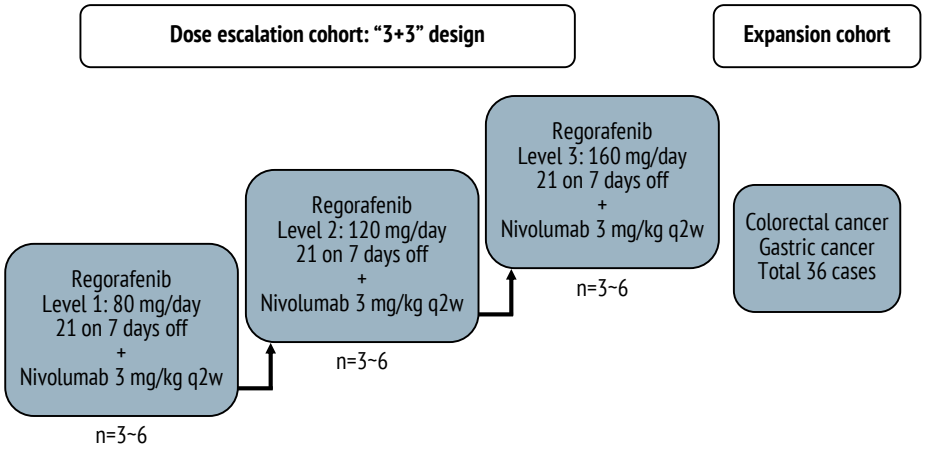
- Colorectal and gastric cancers are among the malignancies with the highest mortality rates worldwide
- Despite improvements in systemic treatment, most patients with metastatic disease will eventually perish from their disease
- Data on immunotherapy for gastric cancer and colorectal cancer have shown limited benefit in non-selected populations (e.g. non-MSI high)
- Pre-clinical data suggest that regulatory T cells (Tregs) and tumour-associated macrophages (TAMs) lead to immune checkpoint antibody resistance
- In murine models:
  - Regorafenib reduced CRC TAMs, and also induced type M1 macrophages
  - Regorafenib showed synergistic activity with anti-PD1 monoclonal antibodies

MSI, microsatellite instability; CRC, Colorectal Cancer

Hoff S, et al. Ann Oncol 2017;28(suppl 5;423); Bray F, et al. CA Cancer J Clin 2018;68(6):394-424; Fukuoka S, et al. J Clin Oncol 2019;37(suppl; abstr 2522); https://www.cancer.org/cancer/stomach-cancer/detection-diagnosis-staging/survival-rates.html; https://www.cancer.org/cancer/colon-rectal-cancer/detection-diagnosis-staging/survival-rates.html

REGONIVO STUDY

STUDY DESIGN



Primary outcome

- Dose-limiting toxicity

Secondary outcomes

- Overall response rate; progression-free survival; overall survival; disease control rate

POPULATION CHARACTERISTICS

Characteristics	Total (n=50)	Dose escalation (n=14)	Dose expansion (n=36)
Median age, years (range)	61 (31–80)	61 (31–77)	61 (41–80)
Male sex	40 (80)	12 (86)	28 (78)
ECOG PS 0	49 (98)	14 (100)	35 (97)
Cancer Type			
Gastric cancer	25 (50)	9 (64)	16 (44)
Colorectal cancer	25 (50)	5 (36)	20 (56)
Site of metastases			
Lymph node	35 (70)	12 (86)	23 (64)
Liver	28 (56)	10 (71)	18 (50)
Lung	22 (44)	5 (36)	17 (47)
Peritoneum	10 (20)	0	10 (28)
Prior regimens, median (range)	3 (2–8)	3 (2–8)	3 (2–8)
Angiogenesis inhibitors	48 (96)	13 (93)	35 (97)
Anti-PD1/PD-L1	7 (14)	4 (29)	3 (9)
HER2 positive in gastric cancer	6 (24)	2 (22)	4 (25)
MSI status			
MSI-H	1 (2)	1 (7)	0
MSS	49 (98)	13 (93)	36 (100)
PD-L1 CPS*			
Positive (CPS≥1)	18 (41)**	3 (25)**	15 (47)**
Negative (CPS<1)	26 (59)**	9 (75)**	17 (53)**

*PD-L1 IHC 28–8 pharmDx CPS; Combined positive score
**Percentage among evaluable patients

Data are n (%) unless otherwise specified

ECOG PS, Eastern Cooperative Oncology Group; MSI-H, microsatellite instability-high; MSS, microsatellite stable; DLT, Dose Limiting Toxicity; ORR, Overall Response Rate; PFS, Progression-free Survival; OS, Overall Survival; DCR, Disease Control Rate

Fukuoka S, et al. J Clin Oncol 2019;37(suppl; abstr 2522)

REGONIVO STUDY

GI connect
POWERED BY COR2ED

PRIMARY OUTCOME

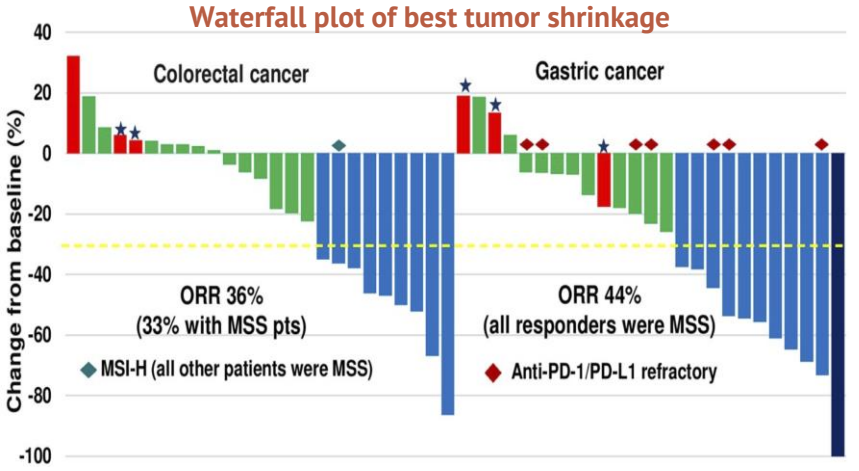
Dose Schedule	Patients Enrolled	Number of Patients with DLTs	DLTs
Regorafenib 80 mg/day + Nivolumab 3 mg/kg	4	0	None
Regorafenib 120 mg/day + Nivolumab 3 mg/kg	7	0	None
Regorafenib 160 mg/day + Nivolumab 3 mg/kg	3	3	Grade 3 Rash, n=1 Grade 3 Proteinuria, n=1 Grade 3 Colonic perforation, n=1*

One patient was excluded from DLT evaluation in each of the regorafenib 80 mg and 120 mg groups
*Reconsider causal relationship at data cut-off

Dose escalation cohort
Maximum Tolerated Dose and Recommended Dose
→ **120 mg of Regorafenib**

Expansion cohort
20% rate of grade 3 skin toxicity with 120 mg (vs. 0% with 80 mg)
→ **80 mg of Regorafenib**

SECONDARY OUTCOMES



Outcome	Colorectal	Gastric
ORR (%)	36	44
Median PFS (months)	6.3	5.8
DCR (%)*	88	88
⩾ Grade 3 toxicity (%)		
80 mg	27	
120 mg	44	
160 mg	100	

*DCR values are for the overall cohort and not stratified by tumor type

DCR, disease control rate; DLT, dose-limiting toxicity; MSI-H, microsatellite instability-high; MSS, microsatellite stable; ORR, overall response rate; PFS, progression-free survival; MTD, Maximum Tolerated Dose; RD, Recommended Dose

Fukuoka S, et al. J Clin Oncol 2019;37(suppl; abstr 2522)

REGONIVO STUDY

GI connect
POWERED BY COR2ED

Translation into clinical practice

- Evidence of clinically significant activity of the combination of a checkpoint inhibitor plus a tyrosine kinase inhibitor in a non-selected population of patients with colorectal cancer and gastric cancer
- Toxicity was manageable using the 80 mg dose of regorafenib
- Encouraging activity as shown by the high response rate in a population of heavily pre-treated patients
- Response rate was not dependent on PD-L1 expression
- In patients with gastric cancer, all patients considered to have disease refractory to anti-PD1/PD-L1 antibodies derived benefit from the combined treatment
- Further assessment of the activity of nivolumab plus regorafenib in a randomised controlled scenario is certainly warranted

Fukuoka S, et al. J Clin Oncol 2019;37(suppl; abstr 2522).

REACH GI CONNECT VIA TWITTER, LINKEDIN, VIMEO AND EMAIL OR VISIT THE GROUP'S WEBSITE

http://www.giconnect.info

Follow us on Twitter
@giconnectinfo

Join the
GI CONNECT
group on LinkedIn

Watch us on the
Vimeo Channel
GI CONNECT

Email
antoine.lacombe@cor2ed.com

GI connect
POWERED BY COR2ED

GI CONNECT
Bodenackerstrasse 17
4103 Bottmingen
SWITZERLAND

Dr. Antoine Lacombe
Pharm D, MBA
Phone: +41 79 529 42 79
antoine.lacombe@cor2ed.com

Dr. Froukje Sosef
MD
Phone: +31 6 2324 3636
froukje.sosef@cor2ed.com