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JournalClub

L'importanza della ricerca in Oncologia

10-11 OTTOBRE 2019 - ROMA

VOI Donna Camilla Savelli Hotel - Via Garibaldi, 27

La ricerca clinica in Italia e in Europa: Studi in corso. aMANTRA STUDY

DISCUSSANT: A. Falcone, M. Scartozzi

GOIRC
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IRCCS Istituto in tecnologie avanzate e modelli assistenziali in oncologia

OECI CLINICAL Cancer Centre

α-MANTRA STUDY

Phase II randomized study of maintenance regorafenib vs placebo in no progression patients after first-line platinum and fluoropyrimidines based chemotherapy in HER2 negative locally advanced/metastatic gastric or gastroesophagel junction cancer

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SOC Oncologia Medica

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BACKGROUND

- 78-80% advanced gastric or GEJ adenocarcinoma HER-2 no amplified -> NO TARGETED therapies.

- Standard chemotherapy in first line with double or triple cytotoxic chemotherapy regimens with OS = 7-11 months compared to BSC.

- Only 45% of the population is eligible for second-line treatment, reinforces the need to extend the time to progression in the subgroup of patients with stable disease after first line chemotherapy.

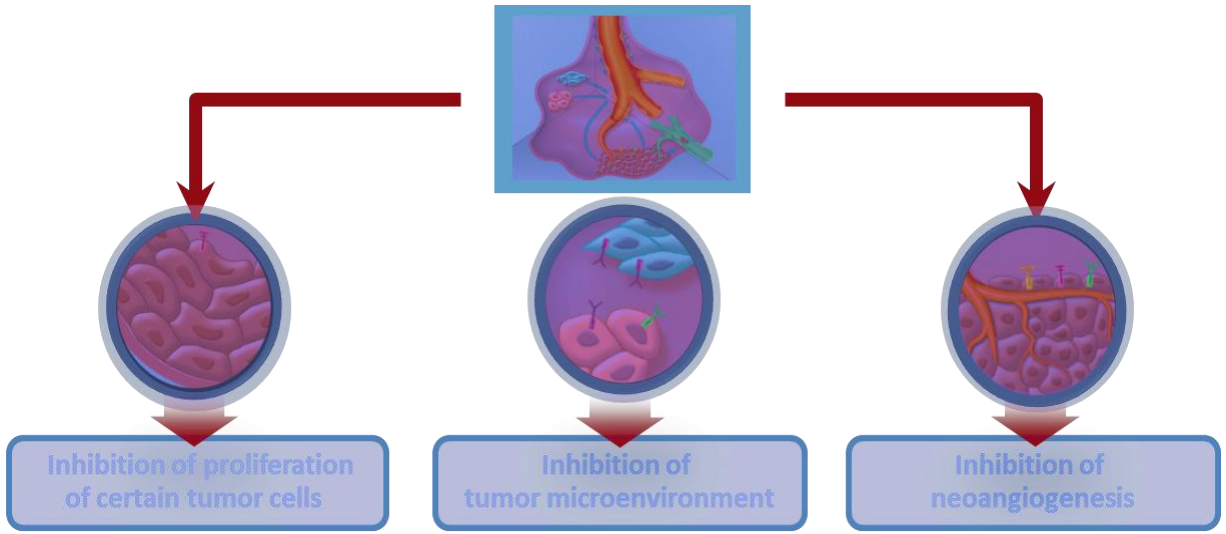
BACKGROUND AND RATIONALE

- The angiogenic upregulation is correlated to poor prognosis and survival in gastric cancer patients.

- Upregulation of *VEGF-VEGFR* signaling axis (endothelial cell growth, migration, and survival from preexisting vasculature, vessel permeability).

- Balance between *Angiopoietin 1* (promoting cell death and disrupting vascularization), and *Angiopoietin 2* (vessel maturation, adhesion, migration, and survival) is important in neoangiogenesis process.

REGORAFENIB – MECHANISM OF ACTION



Regorafenib is an oral multikinase inhibitor and deactivates tumors across three dimensions:

- Angiogenesis (VEGFR1-3, TIE2)
- Oncogenesis (KIT, PDGFR, RET)
- Stromagenesis (PDGFR-β, FGFR)

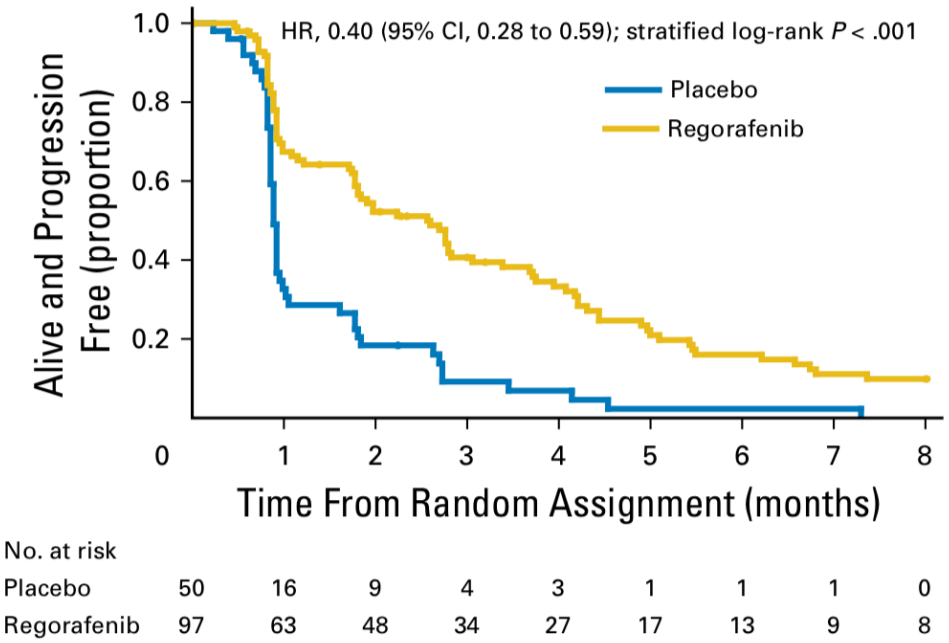
Biochemical Activity	IC_{50} mean ± SD nmol/l (n)
VEGFR1	13 ± 0.4 (2)
Murine VEGFR2	4.2 ± 1.6 (10)
Murine VEGFR3	46 ± 10 (4)
TIE2	311 ± 46 (4)
PDGFR-β	22 ± 3 (2)
FGFR1	202 ± 18 (6)
KIT	7 ± 2 (4)
RET	1.5 ± 0.7 (2)
RAF-1	2.5 ± 0.6 (4)
B-RAF	28 ± 10 (6)
$B\text{-}RAF^{V600E}$	19 ± 6 (6)

Wilhelm SM, et al. Int J Cancer. 2011,129:245-255. Mross K, et al. Clin Cancer Res. 2012;8:2658-2667. Strumberg D, et al. Br J Cancer. 2012;106:1722-1727.

INTEGRATE STUDY

VOLUME 34 · NUMBER 23 · AUGUST 10, 2016

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT



Pavlakis et al, JCO 2016

Regorafenib for the Treatment of Advanced Gastric Cancer (INTEGRATE): A Multinational Placebo-Controlled Phase II Trial

Nick Pavlakis, Katrin M. Sjoquist, Andrew J. Martin, Eric Tsobanis, Sonia Yip, Yoon-Koo Kang, Yung-Jue Bang, Thierry Alcindor, Christopher J. O'Callaghan, Margot J. Burnell, Niall C. Tebbutt, Sun Young Rha, Jeeyun Lee, Jae-Yong Cho, Lara R. Lipton, Mark Wong, Andrew Strickland, Jin Won Kim, John R. Zalcberg, John Simes, and David Goldstein

Treatment	No.	PFS (weeks)	HR
Regorafenib	97	**11.1**	0.41 (95%CI 0.28-0.59) p<0.0001
Placebo	50	**3.9**	

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INTEGRATE II STUDY - ONGOING

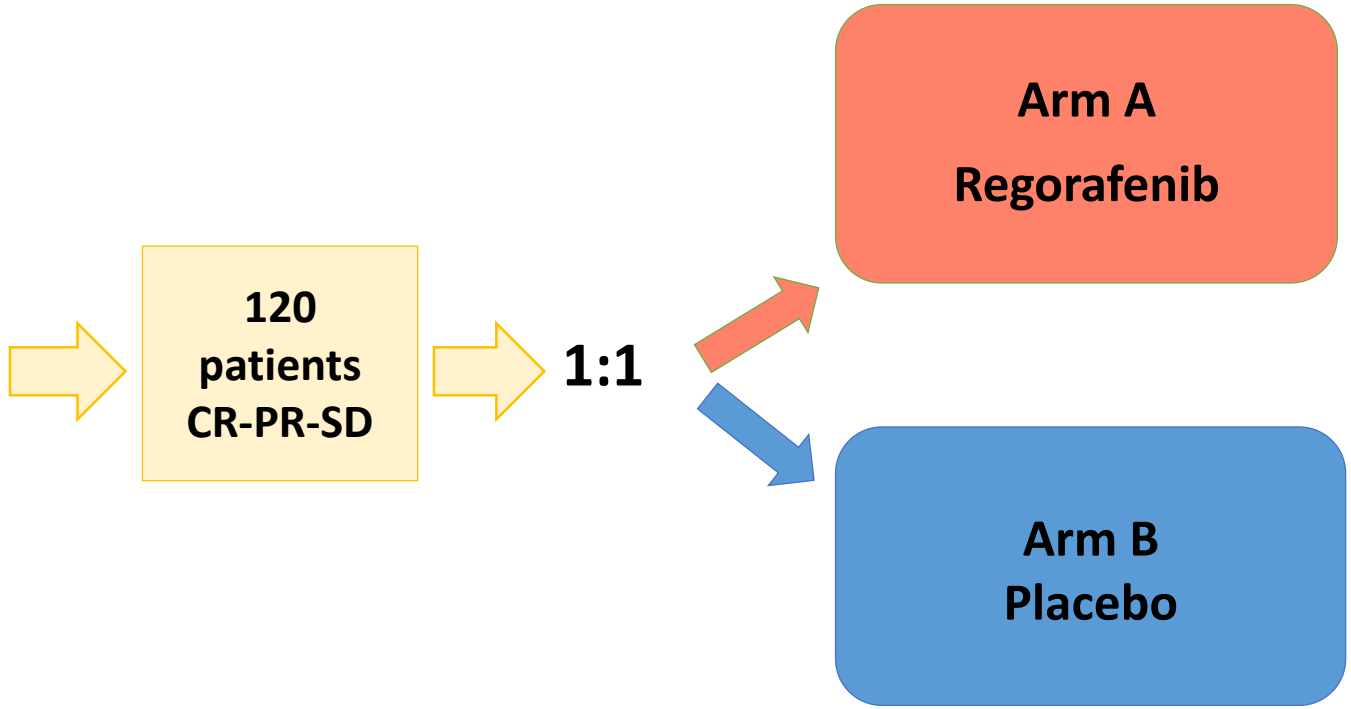
- A Randomised (2:1) Phase III Double-Blind Placebo-Controlled Study of Regorafenib in Refractory Advanced Gastro-Oesophageal Cancer (AGOC)- NCT02773524

Recruitment Status ICMJE	Recruiting
Estimated Enrollment ICMJE **(submitted: May 12, 2016)**	350
Estimated Study Completion Date ICMJE	December 2021
Estimated Primary Completion Date	May 2020 (Final data collection date for primary outcome measure)

clinicaltrials.gov

a-MANTRA: Randomized Phase II Study, double-blind, placebo-controlled

- **Advanced gastric or GEJ cancer HER-2 negative**
- **I line with doublet chemotherapy with platinum compounds and fluoropyrimidines:**
  1. **DDP-5FU/cape (up to 6 cycles)**
  2. **FOLFOX (up to 12 cycles)**
  3. **XELOX (up to 8 cycles)**



PRIMARY endpoints

- PFS (HR 0.57; from 4 to 7 months)

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a-MANTRA: STUDY DESIGN

- The patients after a maximum of 4 weeks after the last cycle of chemotherapy will be randomized (1:1) between:
  - **Arm A 60 patients: Regorafenib 160 mg (4 tablets), given once daily, on a 3-weeks-on/1-week-off dosing schedule**
  - **Arm B 60 patients: Placebo (4 tablets, matching regorafenib tablets in appearance), given on the same schedule**
- The treatment in both arms will perform until intolerance or progression disease

a-MANTRA: STRATIFICATION

- Esophageal-gastric junction vs. distal stomach
- Intestinal subtype vs diffuse subtype
- Locally advanced disease vs metastatic disease
- Peritoneal carcinomatosis vs no peritoneal carcinomatosis

a-MANTRA: STATISTICAL ANALYSIS

- A 1:1 randomization scheme will be used.
- 90% power to detect a HR of 0.57, using a one-sided α-level of 0.10. This corresponds to an increase in median progression free survival **from 4 to 7 months**.
- 118 evaluable enrolled patients and 88 events (progression disease or deaths) occur.
- 120 patients are therefore needed for taking account of possible attrition.
- Recruitment: 24 months

a-MANTRA: MAIN CRITERIA INCLUSION

- Male or female ≥ 18 years of age
- Diagnosis of histologically confirmed adenocarcinoma of the stomach or gastroesophageal junction
- Locally advanced/metastatic gastric or gastroesophageal junction cancer
- HER2 negative gastric or gastroesophagel junction cancer (ICH 0, IHC 1+, IHC + FISH -)
- Have an Eastern Cooperative Oncology Group performance status of 0 or 1 within 14 days prior to the initiation of study treatment
- CR/PR/SD after first-line platinum compound and fluoropyrimidines based chemotherapy
- Measurable disease according to RECIST 1.1 criteria
- Have adequate bone marrow function, liver function, and renal function.

a-MANTRA: MAIN CRITERIA EXCLUSION

- Prior treatment with regorafenib or any other VEGFR-targeting kinase inhibitor
- Prior or concurrent cancer distinct in primary site or histology from *GC or GJC* within 5 years prior to randomization EXCEPT for curatively treated cervical cancer in situ, no-melanoma skin cancer, or superficial bladder tumors classified as noninvasive tumor, carcinoma in situ, or tumor invades lamina propria.

a-MANTRA: OBJECTIVES OF STUDY

- **PRIMARY ENDPOINT:**
  - **Progression Free Survival 1 (PFS1)**

- **SECONDARY ENDPOINTS:**
  - Overall Survival (OS)
  - PFS2 in patients submitted to second line of therapy
  - Safety and tolerability of regorafenib
  - Quality of life (EORTC QLQ-C30)
  - Response Rate (RR)
  - To correlate the genetic mutational profile of the tumors with the RR and the OS

a-MANTRA: COLLATERAL STUDY (optional)

- Tumor tissue analysis:
  - Positivity to EBV by using In Situ Hibridization (ISH)
  - Levels of MSI will be analyzed by Immunohistochemestry (IHC)
  - Analysis of mutations by targeted NGS

- Evaluation of serum biomarkers (e-NOS) (days 1, week 8, 16, 24, 32). Germline DNA will be extracted from a blood sample collected to screen patients for eNOS c.-786C>T and c.894G>T variants by Real Time PCR and automatic sequencing respectively

PARTECIPATING CENTERS:

1	**REGGIO EMILIA**	**PINTO**
2	**ALESSANDRIA**	BELLOTTI
3	**TRENTO**	TRENTIN
4	**BOLZANO**	VICI
5	**VIMERCATE**	FAGNANI
6	**UDINE**	CIARFELLINO
7	**VERONA**	GORI
8	**BOLOGNA (BELLARIA)**	BRANDES
9	**PARMA**	LEONARDI
10	**FERRARA**	FRASSOLADATI
11	**MELDOLA**	FRASSINETI
12	**BOLOGNA (S. ORSOLA)**	DI FABIO
13	**RIMINI**	CARMINATI
14	**PISA**	LEONCINI
15	**GROSSETO**	BENGALA
16	**ANCONA**	BERARDI
17	**PESARO**	CATALANO
18	**FANO**	MATTIOLI
19	PERUGIA	DE ANGELIS
20	FROSINONE	GAMUCCI
21	**ROMA - GEMELLI**	STRIPPOLI
22	**ROMA I.F.O.**	COGNETTI
23	**NAPOLI (UNIVERISITA')**	DE VITA
24	NAPOLI (PASCALE)	CASARETTI
25	**POTENZA**	BILANCIA
26	**RIONERO IN VULTURE**	AIETA
27	BARI	SILVESTRIS
28	**SAN GIOVANNI ROTONDO (FG)**	MAIELLO
29	**BRINDISI**	CINIERI
30	FOGGIA	BISCEGLIE
31	**CATANIA**	BORDONARO

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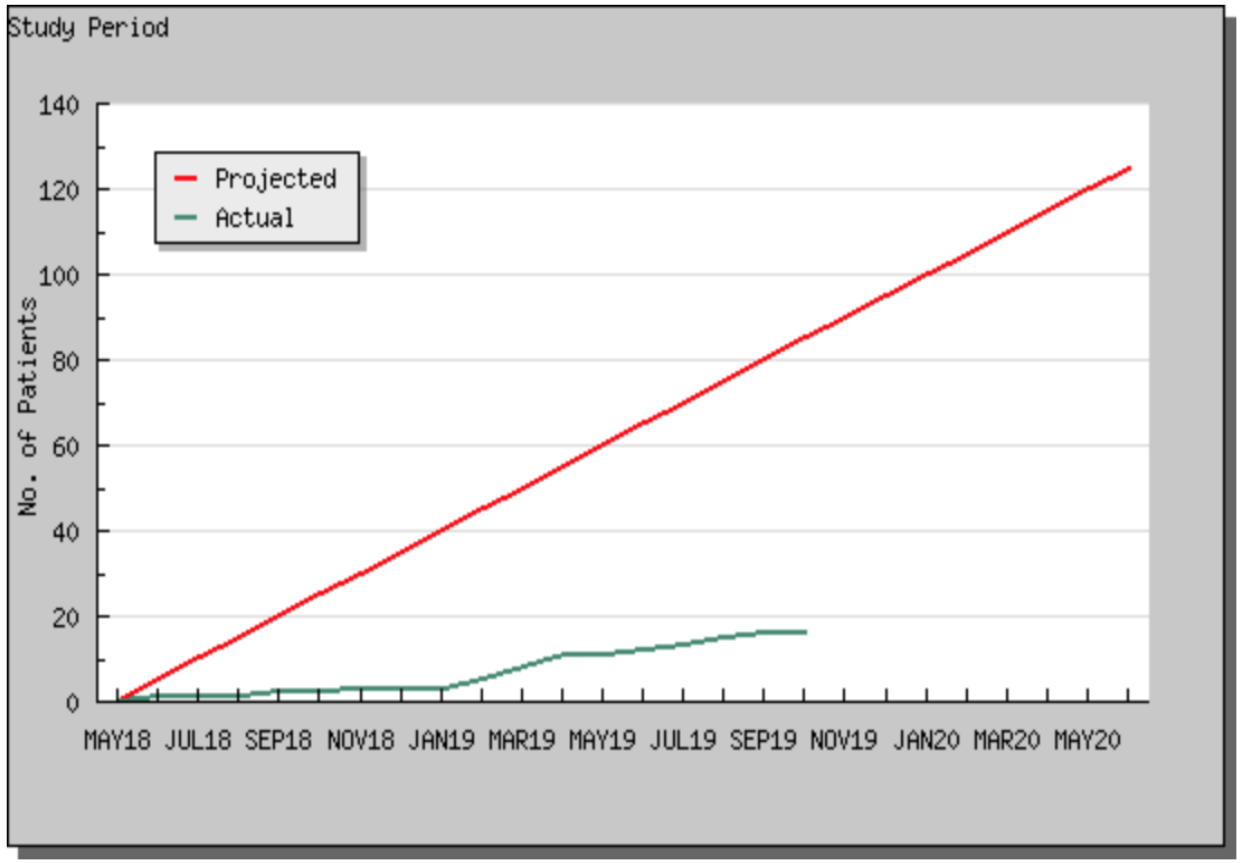
STUDY ACCRUAL SUMMARY

SEPTEMBER, 30 2019

Status	Open	
Opening date	13-JUN-2018	
Closing date	12-JUN-2020	
Accrual duration	731 days	476 days
Number of enrolled patients	120	16
Overall accrual rate	5.0 pts/month	1.0 pts/month
Accrual rate during last three months	1.4 pts/month	

PROJECTED ACTUAL

MONTHLY ACCRUAL REPORT – SEPTEMBER 2019



- ✓ TOTAL ACCRUAL SEPTEMBER: 1
- ✓ TOTAL CENTRES: 9

Highest total accrual	**Highest accrual this month**
POTENZA [BILANCIA]: 4	ALESSANDRIA [BELLOTTI] : 1
ROMA GEMELLI [STRIPPOLI] : 2	--
REGGIO EMILIA [PINTO]: 2	--
RIONERO VULTURE [AIETA] : 2	--
ALESSANDRIA [BELLOTTI] : 2	--

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