LOW GRADE OVARIAN CANCER

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Trials in Low Grade Ovarian Cancer

- LEPRE (ongoing)
- ENGOT-ov60 (ongoing)
- ENGOT-ov70 / ALEPRO (new)

Assemblea MaNGO, Pisa

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LEPRE Trial

Letrozole for Estrogen/Progesterone Receptor positive low-grade Epithelial serous ovarian cancer. A randomized phase III trial

Supported by AIRC Investigator Grant - IG 2018

LEPRE Trial
Rationale - LGSCO

- LGSCO represents approximately 10% of all serous ovarian carcinomas and is classified as a rare cancer
- Retrospective studies highlighted that women with LGSCO are diagnosed at a younger age and experience a longer OS than those with high-grade disease *(Gershenson DM et al. J Clin Oncol. 2015;18;33(24):2675–82.)*
- LGSCO exhibit poor response rates to conventional chemotherapy *(Grabowski JP, et al. Gynecol Oncol. 2016;140(3):457–62.)*
- Estrogen and progesterone play a role in promoting LGSCO progression and ER and PgR are twice as likely to be expressed in LGSCO than in HGSCO *(Wong K-K, et al. Int J Gynecol Pathol. 2007;26(4):404–9.)*
- This provides the rational to evaluate the endocrine therapy efficacy in this setting

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LEPRE Trial
Rationale - Hormonotherapy in LGSCO

- Retrospective studies in both the primary and recurrent settings showed that hormone therapy [utilizing aromatase inhibitors (AIs) or selective estrogen receptor modulator (SERM)] is reasonable and has considerable activity in LGSCO tumors.
- In a retrospective study by the MD Anderson group, 203 women with stage II–IV LGSCO who received hormonal maintenance therapy following primary treatment had a better outcome compared with chemotherapy. Median PFS was 26.4 months with surveillance and 64.9 months with hormonal therapy (P< 0.001).

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ORIGINAL REPORT

Hormonal Maintenance Therapy for Women With Low-Grade Serous Cancer of the Ovary or Peritoneum

David M. Gershenson, Diane C. Bodurka, Robert L. Coleman, Karen H. Lu, Anais Malpica, and Charlotte C. Sun

J Clin Oncol 2017, 1;35(10):1103-1111.

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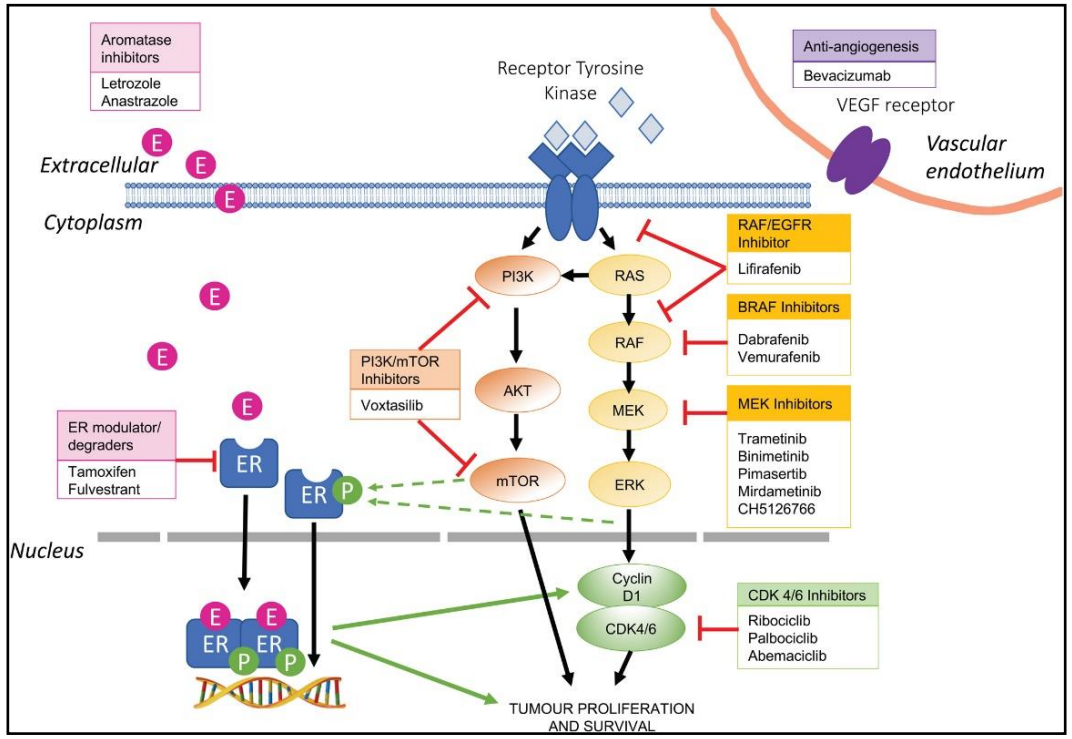
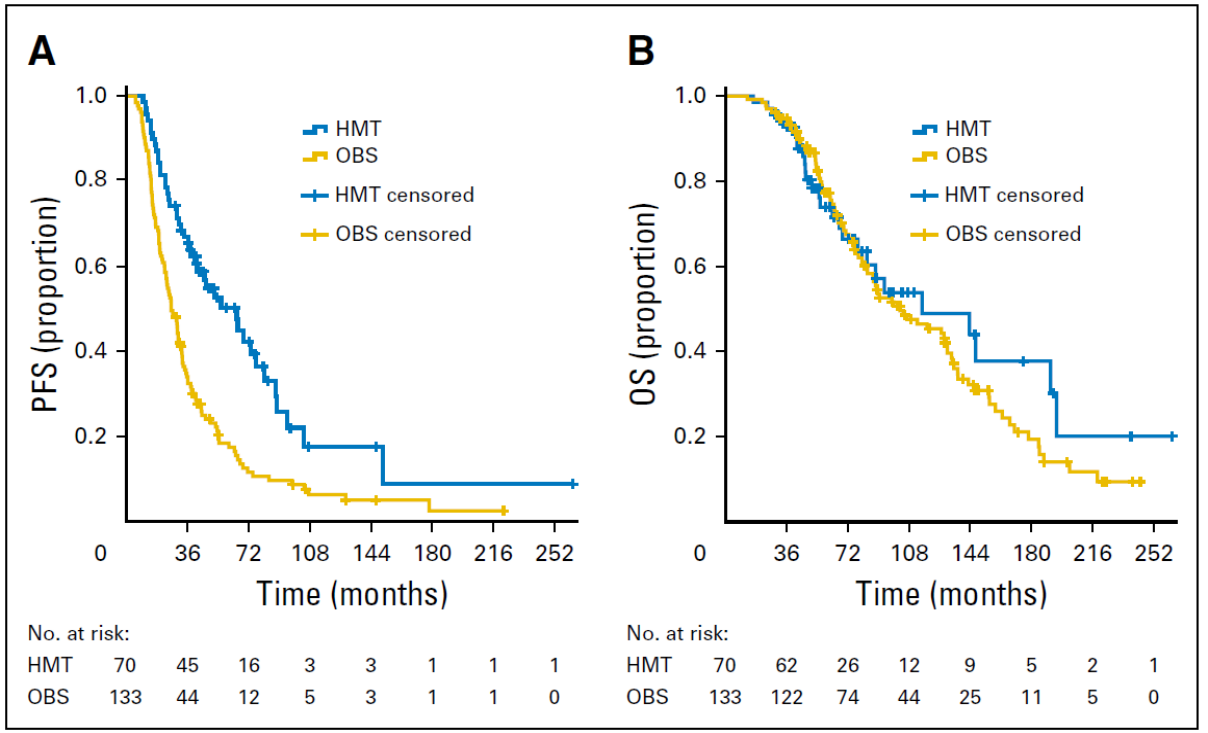
LEPRE Trial
Rationale



Moujaber T, Endocr Relat Cancer. 2021;29:R1-R16



Gershenson DM, J Clin Oncol 2017;35:1103-1111

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National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2019
Low-Grade Serous Carcinoma

NCCN Guidelines Index
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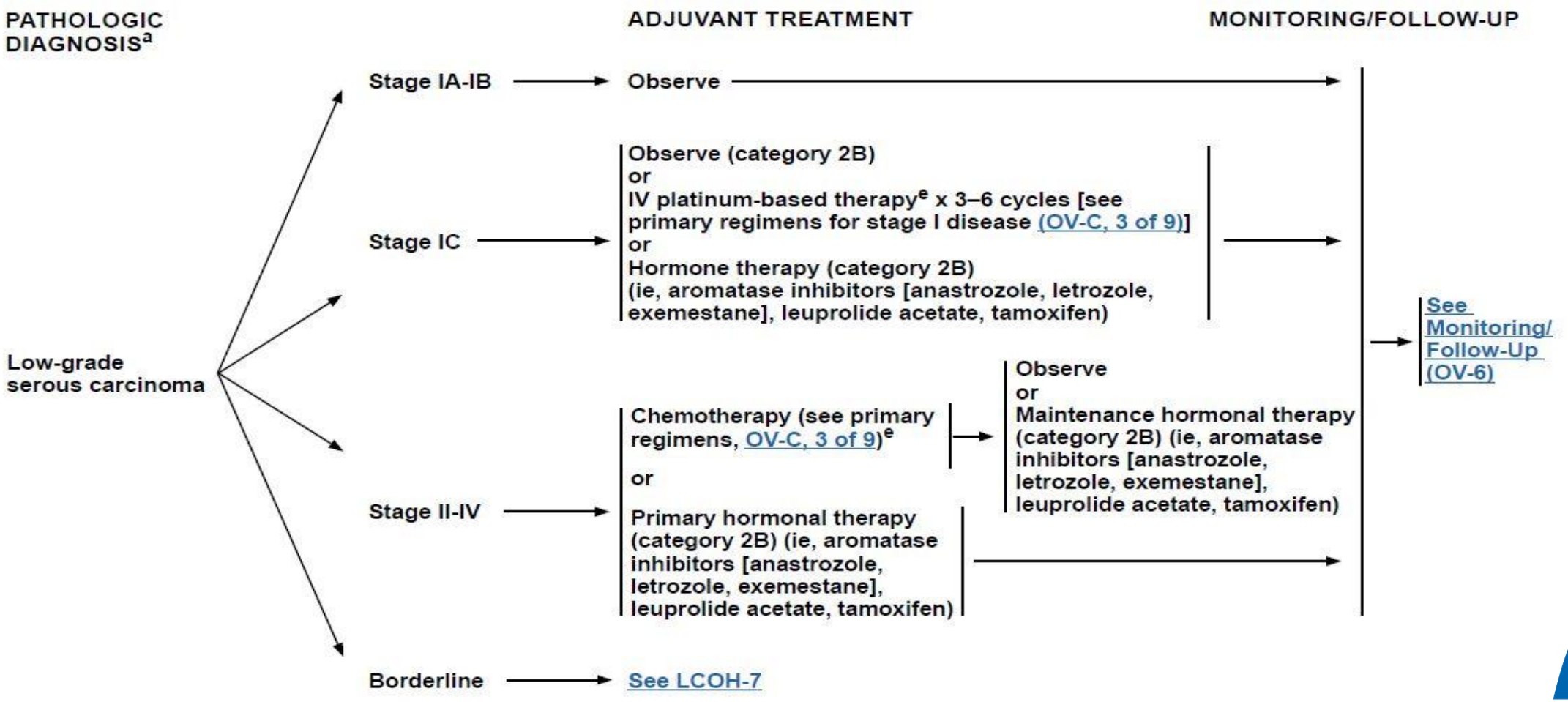

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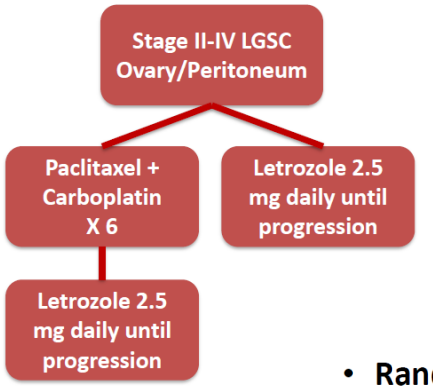
Competitive recruiting studies within ENGOT and GCIG

NRG-GY-019:
Randomized Phase III Trial of Paclitaxel/Carboplatin Followed by Maintenance Letrozole versus Letrozole Monotherapy in Stage II-IV Low-Grade Serous Carcinoma



- Sponsor: NCI (NRG Oncology)
- International phase III trial
- Primary Objective: PFS
- Target: 450 pts

- Randomization: 1:1
- Sample size: 450 patients
- Non-inferiority design
- Primary objective: PFS

ENGOT-ov54 /Swiss-GO-2/MATAO

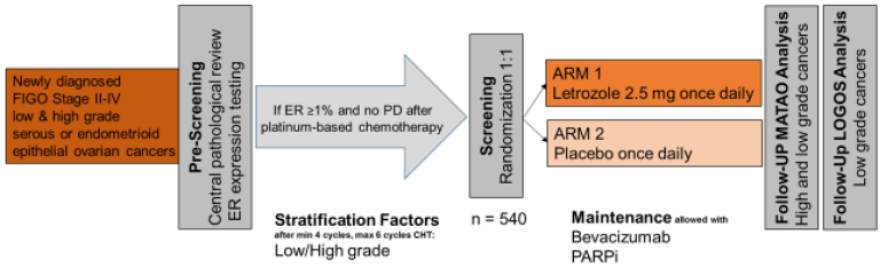
Swiss GO Trial Group

AGO Study Group

MAintenance Therapy with Aromatase inhibitor in epithelial Ovarian cancer: a randomized double-blinded placebo-controlled multi-center phase III Trial (ENGOT-ov54/Swiss-GO-2/MATAO) including LOGOS (Low Grade Ovarian cancer Sub-study)

Trial setting: Newly diagnosed high and low grade serous and endometrioid ovarian cancer FIGO II-IV

Study Design: Randomized double-blinded placebo-controlled multi-center phase III trial
Examining the maintenance therapy with aromatase inhibitor letrozole versus placebo.



Status:	**CH** recruiting, 20/21	since Q4/2020 (241 pat.)
•	**AT** recruiting 5/8	since Q2/2022 (17 pat.)
	DE 27 approved/ 4 initiated/ 3 activated/ 1 recruiting	since Q1/2023 (2 pat.)

LEPRE Trial

Letrozole for Estrogen/Progesterone Receptor positive low-grade Epithelial serous ovarian cancer. A randomized phase III trial

PI: Andrea De Censi
Sponsor: MaNGO

First diagnosis
LGSCO
Stage III-IV
ER+ and/or PgR+
(≥10%)

Upfront **SURGERY** no more than 60 days before randomization

Centralized review of tumor samples

R (1:1)

Experimental arm
Letrozole 2.5 mg daily, per Os, until PD or up to 60 months, whichever comes first

DEXA of the femoral neck *within 3 months of randomization and then every 18 months*.

Total body contrast enhanced **CT-scan and CA-125** every 6 months, until PD

Control arm
Carboplatin AUC 5 + **Paclitaxel** 175 mg/mq, every 21 days, for 6 cycles

At PD,
Patients previously assigned to chemoterapy can receive letrozole and vice versa

Primary Endpoint: PFS
HR=0.5 (mPFS from 24 to 48 mos); 80% power; α=5%; 10% dropout
Accrual 24 months - Follow-up 30 months
Sample-size: 132 patients

Supported by AIRC Investigator Grant - IG 2018

LEPRE Trial
hypothesis and primary objective

Hypothesis

- Letrozole, instead of chemotherapy, as adjuvant treatment in patients with LGSCO stage III-IV, leads to a doubling of median PFS.
- Differences in patients' Quality of Life (QoL) and treatment safety between letrozole group and chemotherapy in favor of letrozole.

Primary objective

- to test the superiority of letrozole in comparison with chemotherapy in terms of time to progression or death (PFS).

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LEPRE Trial
Secondary and Translational objectives

Secondary objectives

- To test whether the expression of ER and PgR is positively associated with the effect of letrozole in terms of PFS and response.
- To evaluate the impact of letrozole on patients' QoL compared with chemotherapy.
- To evaluate the safety of letrozole compared with chemotherapy.
- To describe the OS in order to test the strategy to use chemotherapy or hormone therapy as first line treatment.

Translational objectives

- Since the biological features of LGSCO are only partially elucidated, an additional aim of the project is the full characterization of the mutational and gene expression profile by means of next-generation sequencing (NGS) based methodology.
- To investigate the assessment of circulating (ctDNA) as a tool to monitor tumor response and relapse during the patients follow up.

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LEPRE Trial
Study history

- **2019 January. AIRC approved the study** with the changes requested by the reviewers
- 2021 March. Agreement Mario Negri – Galliera signed on March 2021
- **2022 February. AIFA approved the study after the revisions**
- 2022 September. First two SIV at Brescia Tognon and Genova De Censi
- **2023 February. First patient enrolled by Roma Gemelli site – P.I. Domenica Lorusso**
- **2023 June. Sites involved 39. Active sites 19**

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LEPRE Trial
Accrual at June 2023

City	Principal Investigator	Pts enrolled	Pts on screening	Screening failure	Pts randomized
Roma	Domenica Lorusso	5	0	1	4
Varese	Nicoletta Donadello	1	0	0	1
Meldola	Ugo De Giorgi	1	0	0	1
Brescia	Chiara Abeni	1	0	0	1
	Sum	**8**	**0**	**1**	**7**

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LEPRE Trial
Not enrolling sites (n. 15)

City	Principal Investigator	Days from SIV
Milano	Nicoletta Colombo	7
Roma	Paola Malaguti	14
Ferrara	Antonio Frassoldati	43
Ravenna e Rimini	Claudia Casanova	54
Biella	Laura Zavallone	84
Roma	Violante di Donato	138
Belluno	Fable Zustovich	139
Como	Monica Giordano	158
Arezzo	Sabrina Del Buono	190
Milano	Francesco Raspagliesi	196
Castelfranco V. (TV)	Simona Frezzini	210
Treviso	Grazie Artioli	216
Padova	Valentina Guarneri	221
Genova	Andrea De Censi	278
Brescia	Germana Tognon	285

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LEPRE Trial
Not yet active sites (n. 19)

City	Principal Investigator		City	Principal Investigator
Firenze	Maria Cristina Petrella		Piacenza	Rosa Porzio
Lecco	Federica Villa		Pisa	Angiolo Gadducci
Manerbio	Elena Montani		Prato	Elena Zafarana
Milano	Luca Bocciolone		Reggio Emilia	Alessandra Bologna
Milano	Giovanna Scarfone		Roma	Maurizio Lalle
Modena	Laura Cortesi		Sondrio	Alessandro Bertolini
Monserrato (CA)	Elena Massa		Torino	Dionyssios Katsaros
Monza	Andrea Lissoni		Udine	Claudia Andreetta
Napoli	Michele Orditura		Vercelli	Vincenzo Tortora
Pavia	Chiara Cassani			

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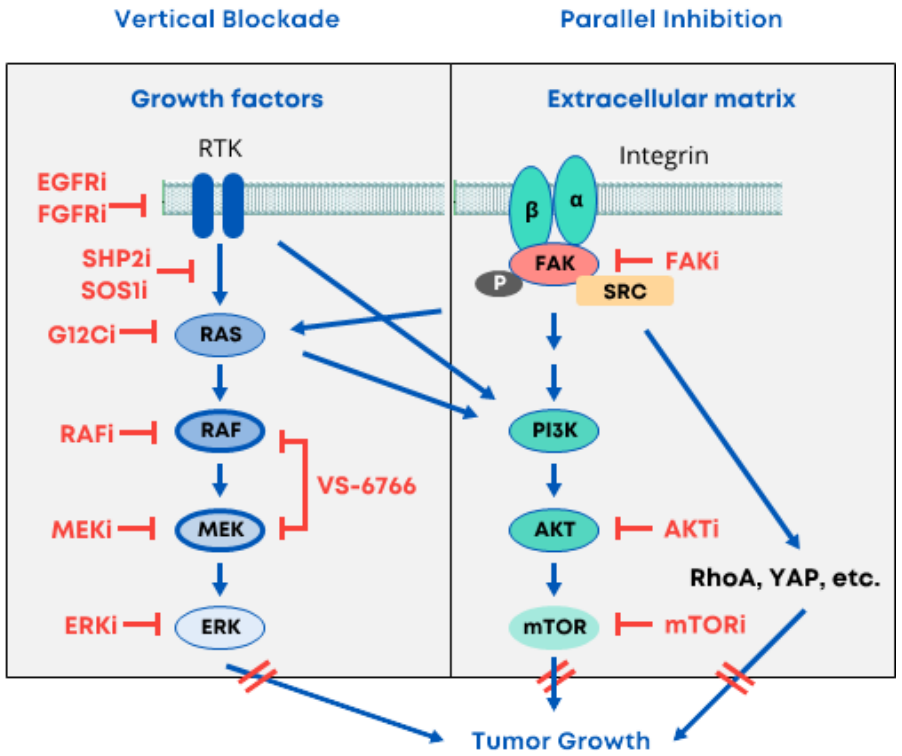
LEPRE Trial
Next steps

- Finalize the study activation by September-October 2023 (7 sites will complete the authorization process by July 2023)

- Expand the study within ENGOT. An invitation to the Spanish group GEICO was recently sent

ENGOT-ov60 / NCRI; GOG-3052
Update June-2022

A Phase 2 Study of VS-6766 (Dual RAF/MEK Inhibitor) Alone and In Combination with Defactinib (FAK Inhibitor) in Recurrent Low-Grade Serous Ovarian Cancer (LGSOC) (RAMP 201)



- MEK inhibitors paradoxically induce RAS signaling by relieving ERK-dependent feedback inhibition of RAK
- MEK inhibitors also cause compensatory activation of FAK
- Single-target therapies are associated with resistance and may not be the best avenue to slowing tumor growth

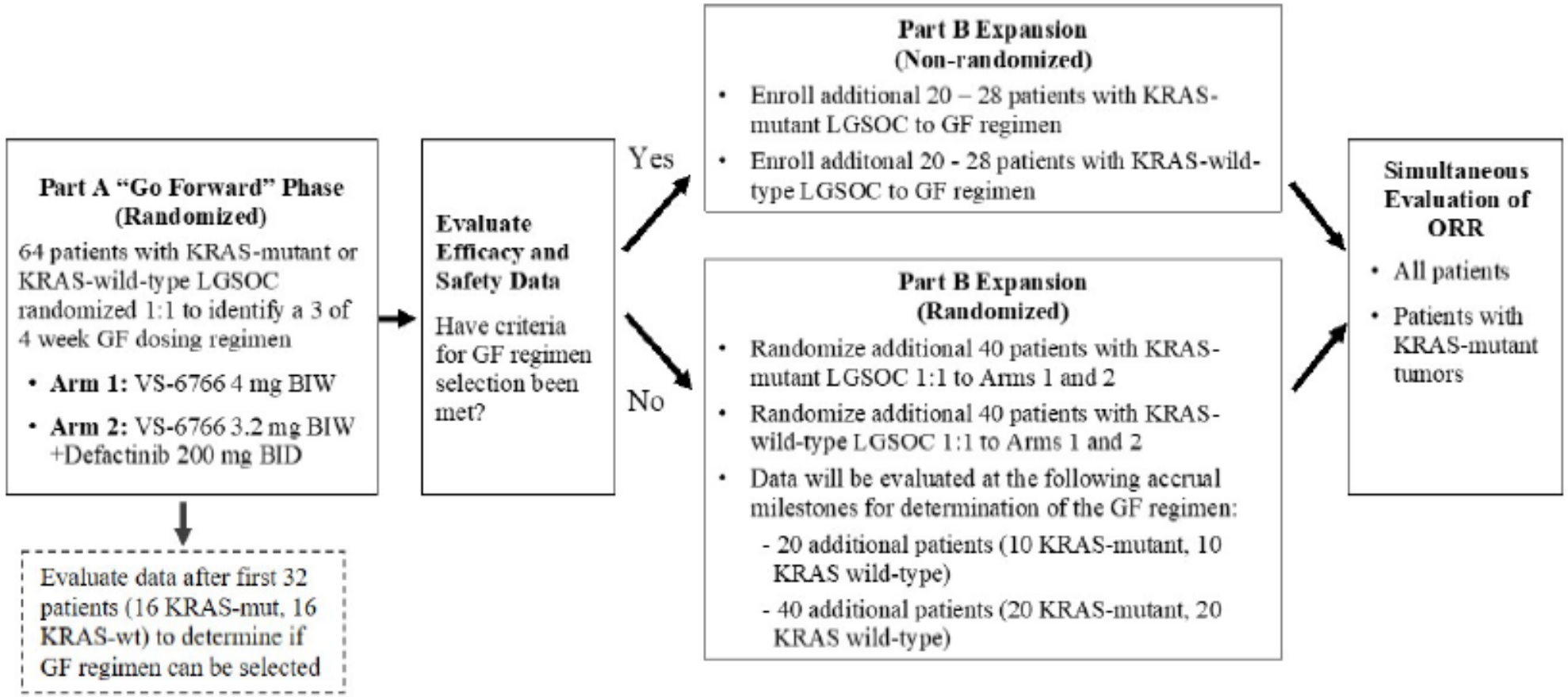
ENGOT-ov60/NCRI; GOG-3052

A Phase 2 Study of VS-6766 (Avutometinib a Dual RAF/MEK Inhibitor) Alone and In Combination with Defactinib (FAK Inhibitor) in Recurrent Low-Grade Serous Ovarian Cancer (LGSOC) (RAMP 201)

- ENGOT Model: C
- Sponsor: Verastem. ENGOT Co-ordinating Unit: The Institute of Cancer Research (NCRI)
- Cooperating ENGOT Groups: BGOG, GEICO, GINECO, MaNGO
- Sites: 45 Globally, inc. GOG, Canada and ENGOT (18 Sites, inc. 2 Sites MaNGO: IEO Milano and IOV Padova)
- Planned No. of Patients (originally): 144; 64 patients Part A and 40-80 patients Part B

ENGOT-ov60/NCRI; GOG-3052

Figure 1: Study Diagram



ENGOT-ov60/NCRI; GOG-3052

Update at June 2023

- 169 patients recruited globally: 102 from GOG US sites and 67 from ENGOT sites.
- Only 2 MaNGO sites were involved (IEO and Padova with 9 patients enrolled)
- Breakdown on recruitment for the Italian sites as of 27-May-2023.
- Waiting for the amendment n. 6, which provides a further extension of enrollment (No more information available).

ALEPRO Trial
ENGOT-ov70

ENGOT
European Network of Gynaecological Oncological Trial groups

Kom op tegen Kanker

BGOG
Belgian Gynaecological Oncology Group

A Phase 2, open label, multicenter study of abemaciclib and letrozole in estrogen receptor-positive rare ovarian cancer

Model A

Study Population:	Recurrent, persistent and/or metastatic ER positive rare ovarian cancer
Study Design:	Subjects with rare ovarian cancer will be enrolled into two cohorts, as follows: • Cohort 1: low-grade serous ovarian cancer • Cohort 2: adult-type granulosa cell tumor
Study Objectives:	Primary Objective: • To determine the overall response rate (ORR) of the combination of abemaciclib and letrozole according to RECIST 1.1 (time frame: 3 years)

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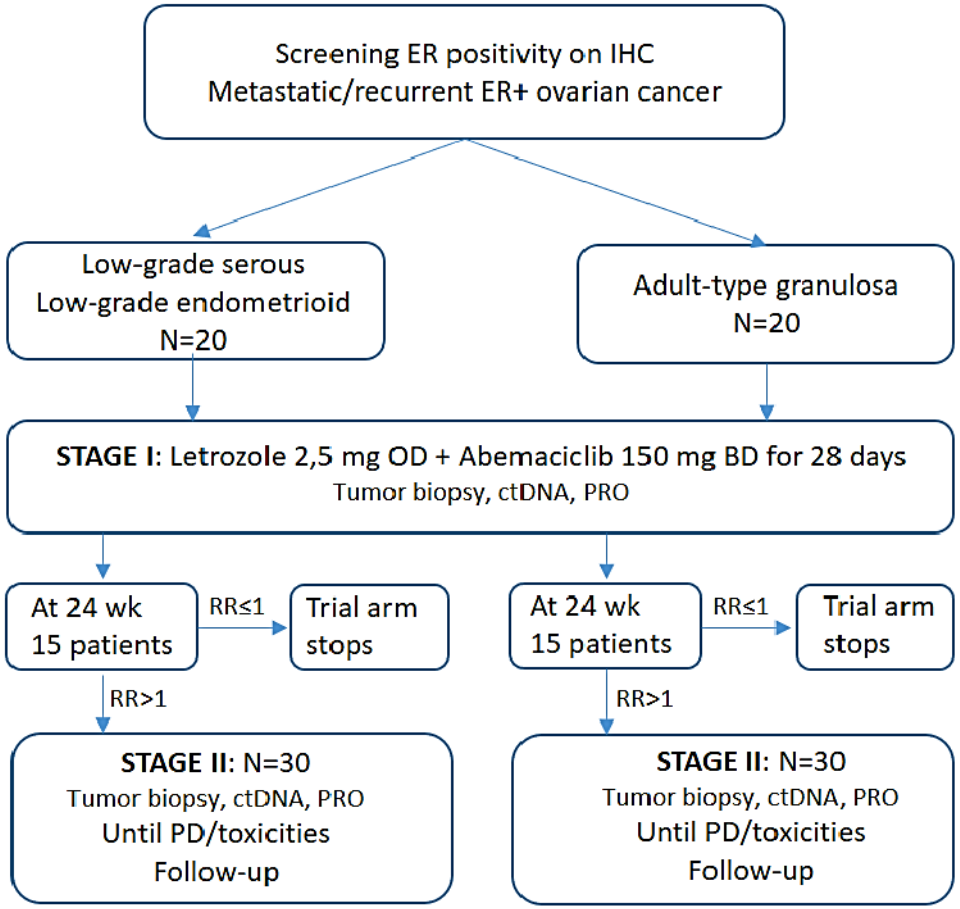
ALEPRO Trial
ENGOT-ov70



ALEPRO Trial
ENGOT-ov70

6 MaNGO sites have expressed interest

Last Sponsor communication on June 15, 2023

Thank you very much for … expressing your interest in the ALEPRO trial.

For now … we are applying for the ATTRACT call … a collaboration of cancer research funding organisations in the following countries: Belgium, the Netherlands, France and Spain.

… when we are planning to include another ENGOT group … we will certainly consider the participation of MaNGO …