LEPRE Trial

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

Elena Biagioli – XVI Assemblea MaNGO
Reggio Emilia, 22 Giugno 2019

Supported by AIRC Investigator Grant - IG 2018

RATIONAL (1)
Low-grade serous carcinoma of the ovary (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

RATIONAL (2)
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 ($P < 0.001$).

VOLUME 35 · NUMBER 10 · APRIL 1, 2017

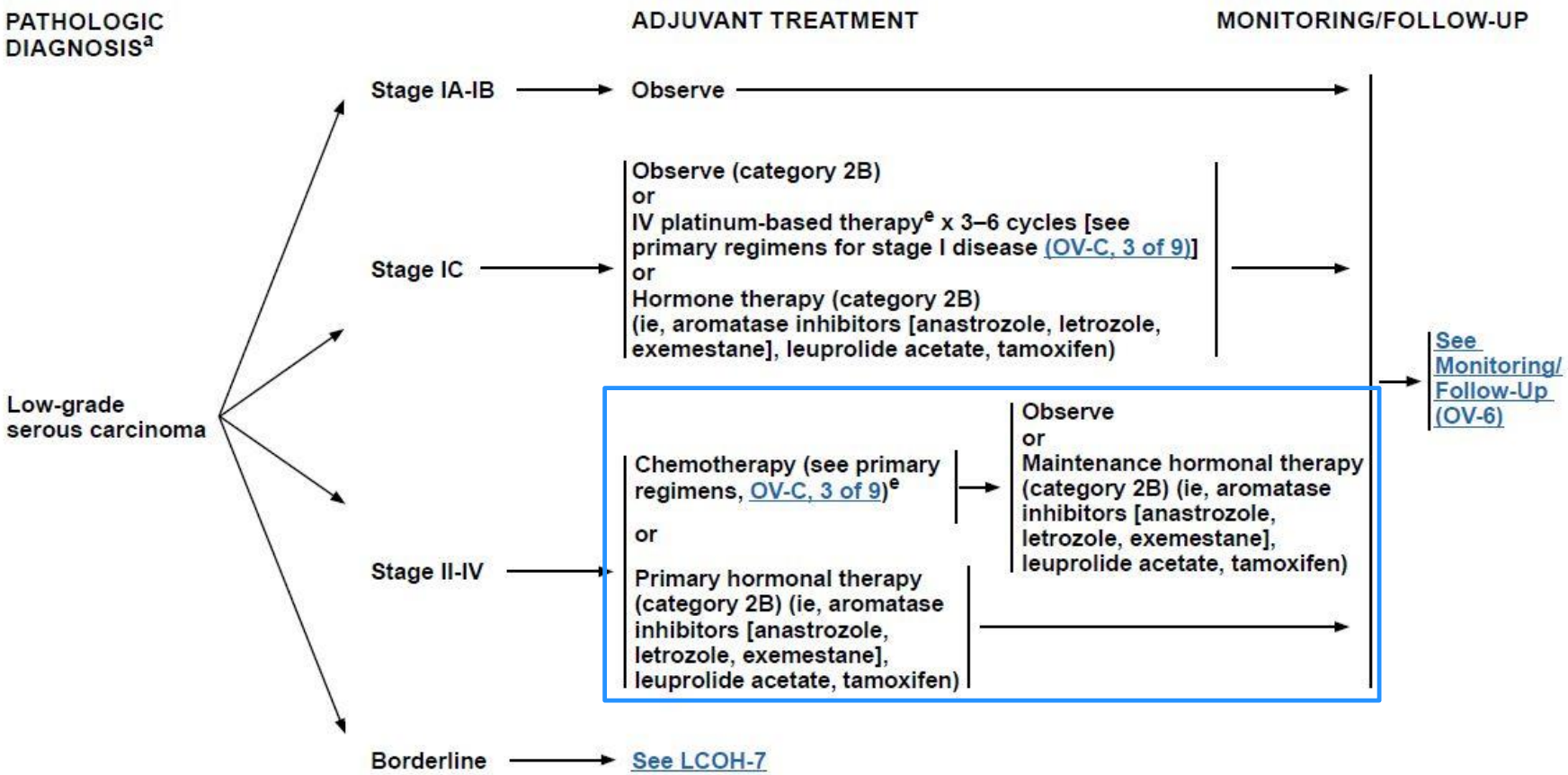
JOURNAL OF CLINICAL ONCOLOGY

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

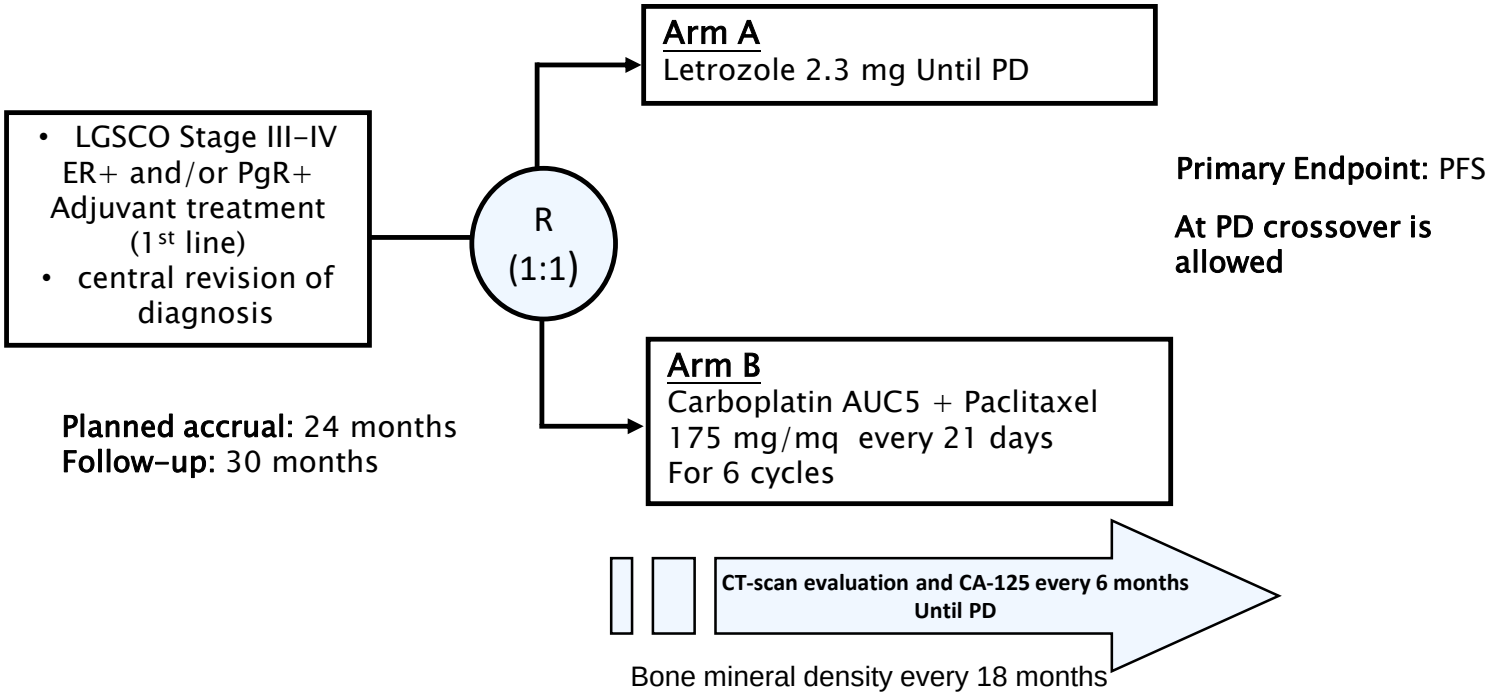
J Clin Oncol 2017, 1;35(10):1103-1111.



[a]See WHO Histologic Classification (OV-E).
[e]See Principles of Systemic Therapy (OV-C) and Management of Drug Reactions (OV-D).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

STUDY DESIGN



Inclusion criteria

- **Stage III-IV LGSCO** (invasive micropapillary serous carcinoma or invasive grade 1 serous carcinoma) of the ovary or peritoneum, all confirmed by a prospective expert pathology panel review at the coordinating centre and differentiated from high grade serous carcinoma via nuclear p53 immunohistochemistry testing.
- Immunoistochemically determined positivity for Progesterone and/or Estrogen receptor expression
- Patients must have undergone an attempt at maximal upfront **cytoreductive surgery**, with either optimal or suboptimal residual disease status allowed.
- Patients must be **postmenopausal or** have undergone a **bilateral salpingo-oophorectomy**.
- **≥18 yrs**. of age.
- **ECOG** performance status of **0, 1**.
- Patients must be **within ≤8 weeks of primary cytoreductive surgery prior to initial randomization**.
- Patients must be **able to take per oral (P.O.) medications**.
- Patients must have **adequate organ and marrow function**
- Patients must have signed an approved **informed consent** and authorization permitting release of personal health information.

Exclusion criteria

- Patients with **concomitant invasive malignancy or a history of other invasive malignancies**, with the exception of non-melanoma skin cancer, are excluded if there is any evidence of other malignancy being present within the past five years. Patients are also excluded if their previous cancer treatment contraindicates this protocol.
- Patients **may not have received neoadjuvant chemotherapy or radiotherapy** for the treatment of this disease.
- Patients **may not have received previous hormonal therapy** for the treatment of this disease.
- Patients with **known hypersensitivity to letrozole or hypersensitivity/intolerance to carboplatin/paclitaxel therapy**.
- Patients receiving chronic treatment with **systemic steroids or another immunosuppressive agent**.
- Patients with **severe cardiac disease**:
  - Myocardial infarction or unstable angina within 6 months prior to registration.
  - New York Heart Association (NYHA) Class II or greater congestive heart failure.
- Patients with **≥grade 2 baseline neuropathy**.

Trial Hypothesis and objectives

The administration of letrozole, instead of chemotherapy, as adjuvant treatment in patients with LGSCO stage III-IV, leads to a doubling of median PFS. Further, we hypothesize to observe differences in patients' Quality of Life (QoL) and treatment safety between letrozole group and chemotherapy in favor of letrozole

Primary objective is to test the **superiority of letrozole** in comparison with chemotherapy in terms of time to progression or death (PFS).

Secondary objectives are:

- 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 the impact of chemotherapy.
- To evaluate the safety of letrozole compared with chemotherapy
- To describe the OS according to randomization arm. As most patients will recur, and since treatment cross over at progression is allowed, we expect no significant difference in OS. Therefore, OS will not be a study endpoint but a valuable indicator to test the overall strategy to use chemotherapy or hormone therapy in the 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.

Moreover, we will investigate:

- the **prognostic and predictive role of androgen receptor** (AR).

- the **assessment of circulating (ctDNA)** as a tool to monitor tumor response and relapse during the patients follow up.

Sample Size

- Median PFS of the control arm: 22-26 month
- HR = 0.5.
- power of 80% and a alpha error of 5% two sided

65 events need to be observed

With 24-month recruitment period and a follow-up of 30 months **108-120** patients need to be randomized

Study organization

Sponsor and Coordinating Centre

- Project Management activities and overall coordination
- Clinical Study preparation
- Clinical trial insurance
- Study treatment packaging, labeling and supply
- Biobanking

Operative Unit 1

- Clinical Data Management System for randomization and e-CRF
- Data-management programs and statistical analysis.
- Submission process to the Regulatory and Ethics Authorities in collaboration with the Sponsor
- Site activation, monitoring and “pharmacovigilance”
- Translational research

Study Update

- January 2019 AIRC approved the study with the changed requested by the reviewers
- 37 Italian sites involved for a commitment of 152 patients
- Negotions with Sophos are ongoing to have Letrozolo for free
- Protocol and study documents are under finalization by Galliera with the revision of Mario Negri Institute
- SC and DSMC will be defined within September
- The submission of the study is planned for October 2019
- The first patient is planned for December 2019