Low-grade serous ovarian cancer (LGSOC) is

DISTINCT and DIFFERENT

Learn why LGSOC needs a different treatment approach

LGSOC Is a Rare Ovarian Cancer That Is Insidious, Persistent, and Ultimately Fatal[1-5]

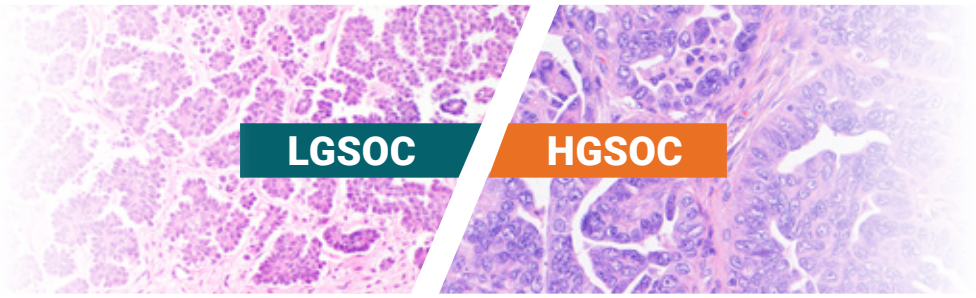
LGSOC is molecularly and histopathologically distinct and clinically different from HGSOC and requires different treatment.[6,7]

- ~90% of patients with LGSOC are **diagnosed at an advanced stage**[3,8]
- LGSOC is **less sensitive to chemotherapy** compared to HGSOC—making treatment more challenging[9-11]
- 80% of patients with LGSOC **experience recurrence**[3,4]
  - On average, patients with LGSOC experienced recurrence in **less than 3 years**[12,13]
- Median overall survival for LGSOC, including younger patients, is **less than 11 years**[4]
- LGSOC **affects a younger patient population** and can disproportionately impact health, fertility, and long-term quality of life[7,8,14]

LGSOC has a bimodal age distribution, **affecting people as young as 20-30** years of age as well as people **50-60 years** of age.[6,15]

The molecular and histopathological distinctions: LGSOC vs HGSOC

LGSOC	HGSOC
HISTOPATHOLOGICAL CHARACTERISTICS	
Mild to moderate nuclear atypia[16]	Tumors are pleomorphic with marked nuclear pleomorphism (>3:1 size variation)[16]
Low mitotic index (12 per 10 high-powered fields)[16]	High mitotic index (≥12 mitoses per 10 high-powered fields)[16]
MOLECULAR CHARACTERISTICS	
TP53 wild type[17]	*TP53* and *BRCA1/2* mutations[15]
KRAS, BRAF, NRAS, and *PIK3CA* mutations[15]	



Low-grade serous cancer shows mild nuclear atypia.[16] High-grade serous cancer is characterized by marked nuclear pleomorphism and abundant mitotic features.[16]

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) recommend both **germline mutation testing and somatic tumor testing** for all patients with ovarian cancer, including LGSOC, at both diagnosis and recurrence.[10,15,18]

The Challenges of Making an Accurate Diagnosis

The **nonspecific symptoms** of LGSOC and **prevalence in younger patients** may contribute to a **delayed diagnosis.**[4,19,20] About 90% of patients are diagnosed with LGSOC at an advanced stage.[3,8]

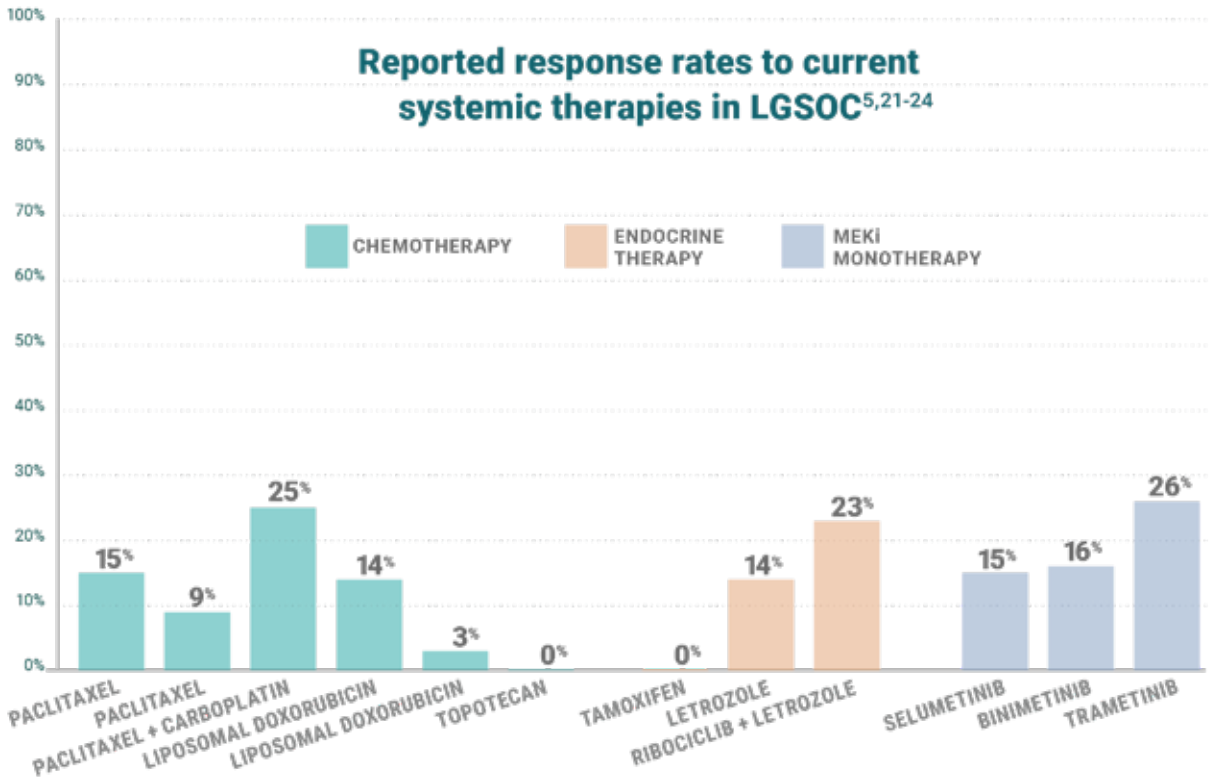
Consultation with a pathologist experienced in evaluating LGSOC is recommended for accurate diagnostic classification.[10]

Quality of Life: an Unmet Need

- There is clearly an unmet need for **more effective and tolerable treatment options** for patients diagnosed with LGSOC[5,21,22]
- The younger patient population living with LGSOC may endure **years of ineffective treatment**[4,5,14,21-23]
- Over 70% of patients report **negative impact on core aspects of their lives,** including mental and physical health, sex life, and overall quality of life[14]
- The biggest **emotional burden** for most patients (~70%) was living every day not knowing if their LGSOC would return[14]

Limitations of Current Management

Currently, patients with LGSOC have inadequate treatment options with **limited efficacy** (ORR 0-26%) and **high discontinuation rates** (up to 36%).[5,10,21-35]



- **LGSOC is less sensitive to chemotherapy** compared to the higher response rate of HGSOC in recurrent settings[9-11]
- **Endocrine therapy** provides moderate efficacy but with a **wide range of toxicities,** including bone-mineral density loss and bone pain—which can be significant with ~36% of patients experiencing bone pain-related problems[10,25-27,29,31,36]
- The **efficacy of MEK-only inhibitors is limited** (ORR 15-26%) with **high discontinuation rates** (over 30% for trametinib and binimetinib)[5,21,23]

With these **suboptimal therapies**, patients may be living for years not only with their cancer but with the **side effects of treatment.**[4,10,25-30]

Exploration of New Pathways and Targets in LGSOC

Recent advances in the biological understanding of the mechanism of disease have opened up **new pathways and targets** for research to explore.[10]

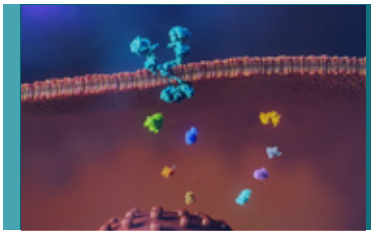
There is no FDA-approved treatment specifically for LGSOC.[37]

LGSOC: A RAS/MAPK-driven cancer[15,38-40]

The RAS (Rat Sarcoma Virus)/MAPK (Mitogen-Activated Protein Kinase) pathway plays a **crucial role** in controlling gene expression, cellular growth, and survival mechanisms, highlighting the need to **optimally target** this critical pathway.[15,38]

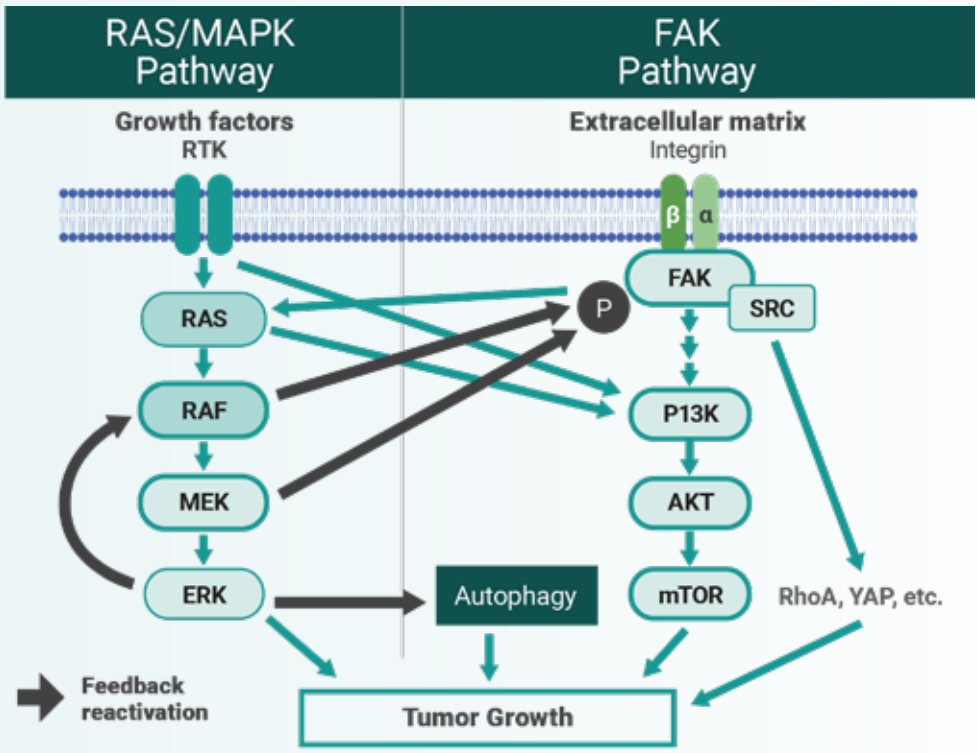
Other important targets being explored for the treatment of LGSOC

In addition to *KRAS* and *BRAF*, **several other genetic alterations are under investigation** for their potential involvement in the pathogenesis of LGSOC. Some of these include *CDKN2A/2B* deletion, *CDK4/6, MEK, NRAS, ERBB2, ERBB3, PIK3CA* alterations, neurofibromin 1 (*NF1*), and chromosome *1p36* deletion.[10,15,41,42]



~70% of patients with LGSOC have **RAS/MAPK pathway-associated mutations,** highlighting the need to optimally target this critical pathway.[15,38-40]

While the RAS/MAPK pathway is promising, ***inhibiting only a single target may cause the reactivation of another oncogene*** on the same pathway—or trigger adaptive resistance with the activation of a parallel pathway.[43,44] Therefore, effective treatment strategies in LGSOC should also ***target key adaptive resistance mechanisms such as FAK.***[45-48]



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LGSOC Is a Rare Ovarian Cancer That Is Distinct and Different

- There is **no FDA-approved treatment** specifically for LGSOC[37]
- Patients with LGSOC have **inadequate treatment options** with limited efficacy, concerning toxicities, and high discontinuation rates[5,10,21-35]
- **Emerging science has opened up new pathways** and targets for research to explore[10]
- **LGSOC is a RAS/MAPK-driven cancer**, highlighting the need to optimally target this critical pathway[15,38-40]

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