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LG-ESSs and HG-ESSs: underlying molecular alterations and potential therapeutic strategies

Key words: low-grade endometrial stromal sarcoma, high-grade endometrial stromal sarcoma, molecular genetics, therapeutics

Research Summary

This review focused on the recurrent genetic and molecular alterations , as well as correspondingly pathogenic mechanisms in LG-ESSs and HG-ESSs.

Based on these known information, shared pathogenic signaling pathways and actionable molecular targets were summarized, and matching therapeutic strategies were proposed.

Proposed therapeutic strategies are critical because systematic therapy for advanced LG-ESSs and HG-ESSs is an unmet clinical need.

Research Summary

Key points listed below

1. Recurrent genetic and molecular alterations

- **LG-ESSs：** ***JAZF1-SUZ12, JAZF1-PHF1, EPC1-PHF1, EPC2-PHF1, MEAF6-PHF, MBTD1-PHF1, BRD8-PHF1, MBTD1-CXorf67***
- **HG-ESSs:** ***YWHAE-NUTM2, ZC3H7B-BCOR, BCOR*** **ITD**
- **The others:** ***CTNNB1*** **activating mutation,**
  CDKN2A **inactivating mutations,**
  amplification of ***MDM2*****,**
  amplification of chromosome 12q13-15

Research Summary

Key points listed below

2. Shared pathogenic signaling pathways, actionable targets, and correspondingly therapeutic strategies

- **Targeting the Wnt pathway and the downstream effectors, particularly CDK4 kinase**
  Examples: CDK4/6 inhibitors alone or combined with the other agents

- **Targeted protein degradation**
  Examples: promsing proteolysis-targeting chimeras (PROTACs)

Research Summary

Key points listed below

2. Shared pathogenic signaling pathways, actionable targets, and correspondingly therapeutic strategies

- **Tyrosine kinase inhibitors**

  Examples: NTRK inhibitors, pazopanib, and imatinib mesylate

- **Targeting epigenetic modification**

  Examples: HDAC inhibitor alone or combined with the other agents