GOG 0281: A RANDOMIZED PHASE II/III STUDY TO ASSESS THE EFFICACY OF TRAMETINIB (GSK 1120212) IN PATIENTS WITH RECURRENT OR PROGRESSIVE LOW-GRADE SEROUS OVARIAN CANCER OR PERITONEAL CANCER

Fast Facts

Trametinib(GSK1120212B) - provided

PATIENT ELIGIBILITY AND EXCLUSIONS

Eligible Patients

1. Patients age greater than 18 with the following tumors are included in the study:
    - Patients initially diagnosed with low-grade serous ovarian or peritoneal carcinoma that recur as low-grade serous carcinoma (invasive micropapillary serous carcinoma or invasive grade I serous carcinomas as defined by GOG, FIGO WHO or Silverberg).
    - Patients initially diagnosed with serous borderline ovarian or peritoneal carcinoma that recur as low-grade serous carcinoma (invasive micropapillary serous carcinoma or invasive grade I serous carcinomas as defined by GOG, FIGO WHO or Silverberg).

2. At least 4 weeks must have elapsed since the patient underwent any major surgery (eg. MAJOR: Laparotomy, laparoscopy, thoracotomy, VATS (video assisted thorascopic surgery). There is no restriction on MINOR procedures: (eg. central venous catheter placement, ureteral stent placement or exchange, tumor core or FNA biopsy).

3. Patients must have documented low-grade serous carcinoma. Confirmation must occur by prospective pathology review prior to study entry (as specified in Section 7.1). The prospective pathology review can be done on tissue from the recurrent carcinoma or from original diagnostic specimen.

4. All patients must have measurable disease as defined by RECIST 1.1. Measurable disease is defined as at least one target lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be $\geq$ 10 mm when measured by CT, MRI, or caliper measurement by clinical exam; or > 20 mm when measured by chest x-ray. Lymph nodes must be > 15 mm in short axis when measured by CT or MRI. All imaging studies must be performed within 28 days prior to registration.

5. Prior therapy
    - Patients must have recurred or progressed following at least one platinum-based chemotherapy regimen.
    - Patients may have received an unlimited number of prior therapy regimens.
    - Patients may not have received all of the five choices in the "standard therapy" arm.
    - Any hormonal therapy directed at the malignant tumor must be discontinued at least one week prior to registration
    - Any other prior therapy directed at the malignant tumor, including chemotherapy and radiation therapy, must be discontinued at least 4 weeks prior to registration. Any investigational agent must be discontinued at least 28 days prior to registration.

6. Trametinib, can cause fetal harm when administered to a pregnant woman. Women of child-bearing potential (i.e. patients whose reproductive organs remain in place and who have not passed menopause) and men must agree to use adequate contraception (e.g. hormonal, intrauterine device or; abstinence1) prior to study entry, during the study participation, and for six months after the last dose of the drug. Women of child-bearing potential must have a negative serum pregnancy test within 14 days prior to

randomization, cannot be breast-feeding, and must agree to use to use a highly effective form of contraception throughout the treatment period and for 6 months after the last dose of study treatment. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. (1Abstinence is only acceptable when this is in line with the preferred and usual lifestyle of the patient.)

7. Patients must have ability to understand and sign an approved informed consent and authorization permitting release of personal health information.

8. Patients must have a GOG Performance Status of 0 or 1.

9. Able to swallow and retain orally-administered medication and does not have any clinically significant gastrointestinal abnormalities that may alter absorption, such as malabsorption syndrome, bowel obstruction, or major resection of the stomach or bowel.

10. All prior treatment-related toxicities must be CTCAE v4 grade <1 (except alopecia) at the time of randomization.

11. Patients must have a left ventricular ejection fraction > lower limit of normal by ECHO or MUGA.

12. Patients must have adequate renal, endocrine, and hepatic function and bone marrow reserve.
    - Serum creatinine ≤1.5 mg/dL *OR* calculated creatinine clearance (Cockroft-Gault formula) ≥50 mL/min *OR* 24-hour urine creatinine clearance ≥50 mL/min
    - Bilirubin ≤ 1.5 times upper limit of normal
    - ALT ≤ 2.5 times upper limit of normal
    - AST ≤ 2.5 times upper limit of normal
    - Albumin ≥ 2.5 g/dL
    - PT and APTT ≤ 1.5 times upper limit of normal
    - Neutrophil count ≥ 1.2 x 109/L
    - Platelet count ≥ 100 x 109/L
    - Hemoglobin ≥ 9.0 g/dL

    Samples must be taken within 14 days prior to treatment.

13. If letrozole is selected as the control therapy, patients must be postmenopausal, either following bilateral oophorectomy or at least 5 years after spontaneous menopause. Patients within 5 years of spontaneous menopause or who have had a hysterectomy without bilateral oophorectomy must have postmenopausal LH and FSH levels. Patients on HRT must agree to withdrawal of hormone therapy before letrozole is started.

Ineligible Patients

1. Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

2. Use of other investigational drugs within 28 days (or five half-lives, whichever is shorter; with a minimum of 14 days from the last dose) preceding the first dose of trametinib or standard of care agent.

3. If patients have had a potential index lesion radiated, it must have progressed post radiation therapy to be used as a measurable eligibility lesion.

4. Patients may not have received prior MEK, KRAS, or BRAF inhibitor therapy.

5. Current use of a prohibited medication. The following medications or nondrug therapies are prohibited:
    - Patients may not be receiving any other anti-cancer or investigational agents.
    - Because the composition, PK, and metabolism of many herbal supplements are unknown, the concurrent use of all herbal supplements is prohibited during the study (including, but not limited to St. John's Wort, kava, ephedra [ma huang], gingko biloba, dehydroepiandrosterone [DHEA], yohimbe, saw palmetto, or ginseng).

6. Patients with known leptomeningeal or brain metastases or spinal cord compression should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

7. Patients with a bowel obstruction or any other gastrointestinal condition that might affect absorption of the oral drug should be excluded. This would include patients with inability to swallow and retain orally administered medication, malabsorption syndrome, or those with a major resection of the stomach or bowels.

8. Patients with a history of interstitial lung disease or pneumonitis.

9. Patients with a previous or current malignancy at other sites should be excluded, with the exception of:
    - Curatively treated local tumors such as carcinoma-in-situ of thecervix, basal or squamous cell carcinoma of the skin
    - Tumors for which no relapse has been observed within 5 years

10. Known Hepatitis B Virus (HBV), or Hepatitis C Virus (HCV) infection (patients with chronic or cleared HBV and HCV infection are eligible). Patients with Human Immunodeficiency Virus (HIV) are not eligible if on anti-retroviral medications.

11. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to drugs chemically related to Trametinib, or excipients, or to dimethyl sulfoxide (DMSO), or to Cremophor EL (polyoxyethylated castor oil). Please note, exclusion for Cremophor is unnecessary unless paclitaxel is the only agent available and the patient randomizes to the conventional therapy option.

12. Patients with a history or evidence of cardiovascular risk, including any of the following:
    - LVEF<LLN
    - QTcB > 480 msec.
    - History or evidence of current clinically significant uncontrolled arrhythmias.
    - Exception: Subjects with controlled atrial fibrillation for > 30 days prior to randomization are eligible.
    - History of (within 6 months prior to randomization) acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty, or stenting.
    - History or evidence of current > Class II congestive heart failure as defined by New York Heart Association (NYHA).
    - Treatment refractory hypertension defined as a blood pressure of systolic >140mmHg and/or diastolic >90mmHg which cannot be controlled by anti-hypertensive therapy
    - Patients with intra-cardiac defibrillators or permanent pacemakers
    - Known cardiac metastases

13. Patients with a history or current evidence/risk of retinal vein occlusion (RVO).

14. Any serious and/or unstable pre-existing medical disorder (aside from malignancy exception above), psychiatric disorder, or other conditions that could interfere with subject's safety, obtaining informed consent or compliance to the study procedures.
15. QT interval. See the table in section 6.28.

16. Animal reproductive studies have not been conducted with trametinib. Therefore, the study drug must not be administered to pregnant women or nursing mothers. Women of childbearing potential should be advised to avoid pregnancy and use effective methods of contraception. If a female patient or a female partner of a patient becomes pregnant while the patient receives trametinib, the potential hazard to the fetus should be explained to the patient and partner (as applicable).

TREATMENT

Active Comparator: Arm A (letrozole, tamoxifen, paclitaxel, PLD, topotecan)

- Patients receive clinician's choice of either letrozole PO QD on days 1-28, tamoxifen citrate PO BID on days 1-28, paclitaxel IV over 1 hour on days 1, 8, and 15, pegylated liposomal doxorubicin hydrochloride IV over 1 hour on day 1, or topotecan hydrochloride IV over 30 minutes on days 1, 8, and 15.
- Courses repeat every 28 days in the absence of disease progression or unacceptable toxicity. Patients developing progressive disease may cross over to Arm B.

Experimental: Arm B (trametinib)

- Patients receive trametinib PO QD on days 1-28.
- Courses repeat every 28 days in the absence of disease progression or unacceptable toxicity.

PRE-STUDY PARAMETERS (Section 7.0)

- History & Physical
- Serum pregnancy test
- Ophthalmologic Exam / Assessment of visual disorders
- Radiographic disease assessment (CT or MRI of chest, abdomen and pelvis)
- QOL assessments
- Vital signs (including Height/Weight)
- ECG
- Echocardiogram (ECHO)/MUGA
- CBC/Differential/ Platelets
- CMP including Mg, PO4
- PTT, PT/INR
- CA125
- Toxicity Assessment
- Urinalysis
- Digital review of pathology to confirm eligibility