PACES
Preventing Adenomas of the Colon with Eflornithine & Sulindac

SWOG CANCER RESEARCH NETWORK

Frequently Asked Questions (FAQ) for Staff Training Use Only

- Responses approved by Dr. Jason Zell, Principal Investigator

1. What is the maximum time for registration after the patient has their primary resection?

Per protocol Section 5.2b.1, patients must be registered between 120 days and 456 days (inclusive) of primary resection. Patients must show no evidence of colorectal cancer based on post-operative colonoscopy (performed at least 120 days after the colon or rectal resection date and prior to registration). Patients with adenomas detected at the one-year postoperative colonoscopy are eligible if all adenomas have been completely removed.

2. Do enrolling sites get a starter supply of study agent in advance of enrolling patients?

Per protocol Section 3.4a, blinded, patient-specific supplies of eflornithine/placebo and sulindac/placebo will be sent to the registering investigator after the patient is registered and should arrive within 10 days.

3. Is there any odor with the eflornithine tablets that might give away whether a patient is taking the drug or a placebo?

The Pharmaceutical Management Branch is not aware of any odor.

4. Are rectal cancer patients eligible for enrollment in PACES - S0820?

Yes, as of Revision #4, rectal cancer patients are eligible for this study.

5. Is a polypectomy allowed?

Per protocol Section 5.2a.2, a polypectomy may be allowed for Tis (Stage 0) or pT1 patients only under certain conditions. Refer to this section of the protocol for the required criteria for polypectomy for eligibility.

6. Recording the percent of colon surface area visualized during a colonoscopy is not standard at our site. Will this be a problem?

No. This information is of interest for secondary analyses, but if it is not available, then you would not complete that question on the S0820 Colonoscopy Report form.

7. If the colon adenocarcinoma metastasized into the omentum, is the patient eligible?

Cancer that has metastasized to the omentum renders the patient ineligible.

8. We have another study open that involves many colonoscopy reports and have learned our average colonoscope withdrawal time is not greater than 6 minutes. Would these reports still be acceptable?
We realize the 6 minute goal, based on recommendations from a NEJM article, is not always realized. The decision on whether colonoscopy is successful is made by the treating physician/ gastroenterologist. We want to record withdrawal time and key landmarks but they are not eligibility requirements.

9. What type of audiometry is required for S0820?
Per protocol Sections 5.2b.5 and 7.3a, patients must have a pure tone audiometry evaluation to document air conduction performed by an audiologist in a hearing test room with insert earphones.

10. There was hearing loss observed with the eflornithine Phase III trial referenced in protocol Section 2.0 and Section 16, reference 23. Is the hearing loss reversible when the drug is discontinued?
Currently, long-term effects of eflornithine on hearing at the doses investigated here are unknown. Clinical hearing loss wasn't evident in the prior trial of adenoma patients– that is to say patients did not notice they had hearing loss, but audiogram tests detected a 8% loss at some frequencies, which was not statistically significant. We don't have long term results. For this trial, the benefit/risk ratio was seen as acceptable. These drugs are not at that point where we would consider them for healthy patients but this population of CRC survivors has high enough risk to make the benefit/risk ratio acceptable.

11. How are patients with hearing loss going to be protected?
Patients with baseline hearing loss are excluded from trial enrollment. As stated in eligibility criteria Section 5.2b.5, patients with hearing loss > 40 dB in any of the five tested frequencies (250 Hz, 500 Hz, 1,000 Hz, 2,000 Hz, 4,000 Hz) are not eligible.

No clinically significant hearing loss was observed in the prior phase III clinical trial using eflornithine/sulindac vs. placebo for a 3-year intervention in colorectal adenoma patients. The attributable risk of ototoxicity for the combined regimen (8.4%) vs. placebo, and the mean dB hearing loss (<2dB) are considered to be low, particularly when compared to the rates of neurologic toxicity ascribed to chemotherapy that many of these subjects will have already received for their adjuvant treatment (e.g., neurotoxicity rates ascribed to modern adjuvant chemotherapy regimens are as follows: Grade 1 = 85%; Grade 2 =32% Grade 3= 8%; Kuebler, JP et al, *J Clin Oncol* 25(16): 2198-2204; Land SR et al, *J Clin Oncol* 25(16):2205-2211). Additionally, the population under study, namely - colon adenocarcinoma patients, is considered to be at risk for multiple cancer-related events (including local cancer recurrence, new adenoma formation, high-risk adenoma formation, new 2nd primary colon adenocarcinoma incidence, distant recurrence, cancer-specific mortality). Thus the low risk of subclinical (Grade 0) ototoxicity ascribed to the regimen has been deemed acceptable by the S0820 study investigators, given the overall risk-to-benefit ratio. No additional audiograms are included as part of the routine monitoring in this study, however if patients do experience *clinical hearing loss* (i.e., an unexpected event, based on the current literature), or any other unexpected clinical event, for that matter - then additional workup and evaluation would be indicated (and not covered routinely as part of S0820).

12. Is there funding available for the baseline audiogram?
Per the S0820 funding memo, federal funds are available to all NCORP and Non-NCORPs for submission of the S0820 Audiometry Evaluation form after a patient is registered to the study. $125 is available for each of two required audiograms for the trial.. Audiometry exam screen failures will also be reimbursed. See the S0820 Funding Memo available on the S0820 Protocol Abstract page for more information.

13. Are statins allowed?
Yes, statins are allowed while the patient is participating in this study.

14. Is cardiovascular monitoring required as part of the study? Why not?
In a prior phase III clinical trial, no statistically significant differences in cardiovascular (or gastrointestinal) adverse events were observed between combination eflornithine/sulindac and placebo. As an added measure to ensure safety of study subjects, patients with certain cardiovascular conditions are not eligible. As stated in Eligibility Criteria 5.2, patients must not have cardiovascular risk factors including unstable angina, history of documented myocardial infarction or cerebrovascular accident, coronary artery bypass surgery, or New York Heart Association Class III or IV heart failure. Patients must not have known uncontrolled hyperlipidemia (defined as LDL-C ≥ 190 mg/dL or triglycerides ≥ 500 mg/dL) within the last 3 years prior to registration or uncontrolled high blood pressure (systolic blood pressure > 150 mm Hg) within 28 days prior to registration. (A table of New York Heart Association Classifications is included in Appendix 19.6.)