Alliance A221504:
A Randomized, Double-Blind, Placebo-Controlled Pilot Study of an Oral, Selective Peripheral Opioid Receptor Antagonist in Advanced Non-Small Cell Lung Cancer

Pankaj Gupta, MD

VA Long Beach Health Care System, Long Beach, CA

TAP TO RETURN TO KIOSK MENU

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Rationale

Opioid medications are the mainstay of treatment for severe, chronic cancer pain. The analgesic activity of opioids is mediated via central mu opioid receptors (MORs) in the central nervous system. However, MORs are also present on endothelial cells and in human tumors (**peripheral** MORs), including lung cancer. Expression and activation of peripheral MORs are associated with tumor progression in animal models. Recent clinical studies raise the possibility that opioid exposure is also associated with tumor progression in patients with various malignancies including lung cancer. Symptoms related to progression of cancer and its treatments, as well the adverse effects of opioids, all contribute to impair the health-related quality of life (HRQoL). One recent trial studied people with very advanced cancers who were constipated from opioids. Those who got a medication that blocks unwanted peripheral opioid effects lived significantly longer than patients who did not get the medication. **However, it is NOT known if opioids stimulate cancer growth in people.**

Our long-term goal is to develop a novel, non-chemotherapeutic intervention blocking the activation of peripheral opioid receptors that contributes to tumor progression and adverse effects of opioids. This may improve the HRQoL of patients with advanced malignancies, and may also improve disease outcomes. Towards this eventual goal, we will perform this pilot study to first determine the feasibility and safety of long-term administration of an orally available, FDA-approved, peripherally acting mu opioid receptor antagonist (PAMORA) in a patient population receiving standard chemotherapy for advanced, incurable lung cancer.

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Objectives

Primary

- To determine feasibility and safety of long-term administration of naloxegol in patients with advanced NSCLC receiving first-line systemic therapy

Secondary

- HRQoL
- Pain levels and analgesic requirements
- Opioid adverse effects
- Progression free survival (PFS) and overall survival (OS)
- Chemotherapy discontinuation rate due to AEs
- Deaths attributable to chemotherapy

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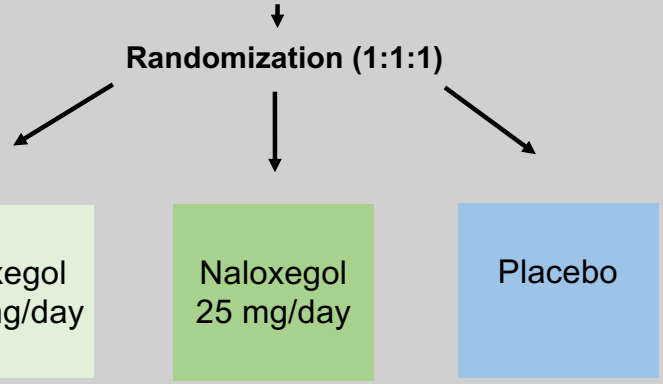
Study Schema

Baseline data, registration
Baseline blood sample. Existing biopsy slides for correlative studies



Data collection every 3 weeks for 1 year (at clinic visit or by mail).
Blood samples: once at 3 and 6 weeks from initiation of study treatment
N = 204. Study duration 2 years

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Treatment Plan

Bottle 1 "12.5 mg"	Bottle 2 "25 mg"	Naloxegol Dose
12.5 mg Naloxegol	25 mg Placebo	12.5 mg
12.5 mg Placebo	25 mg Naloxegol	25 mg
12.5 mg Placebo	25 mg Placebo	0 mg

Take one pill from each of the two bottles, once every day

Naloxegol is **FDA approved** for opioid-induced constipation. **Does not interfere with pain relief** from opioids. Generally well tolerated. Stored at room temperature. **It is not a controlled substance**. Naloxegol and placebo are **provided by AstraZeneca**. Standard evaluation, cancer treatment, and monitoring of advanced lung cancer should be **billable** to Medicare/insurers, per CTSU.

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Eligibility Criteria

- Patients with stage IIIB or IV (AJCC 7th ed) non-small cell lung cancer **(NSCLC: any subtype)** starting **any first-line systemic therapy of the investigator's choice**
- No **known** EGFR or EML4-ALK driver mutations (no need to test just for this study)
- Maintenance treatment OK. Prior adjuvant chemo/radiation, palliative radiation OK
- Performance status ECOG 0-2
- **Some opioid use (no minimum amount)** at some time during 4 weeks prior to registration: see list of allowed and prohibited opioids
- Patients with treated brain metastases eligible
- **A221504 does not prohibit patients from participating concurrently in another study/trial,** as long as the other trial allows participation in A221504

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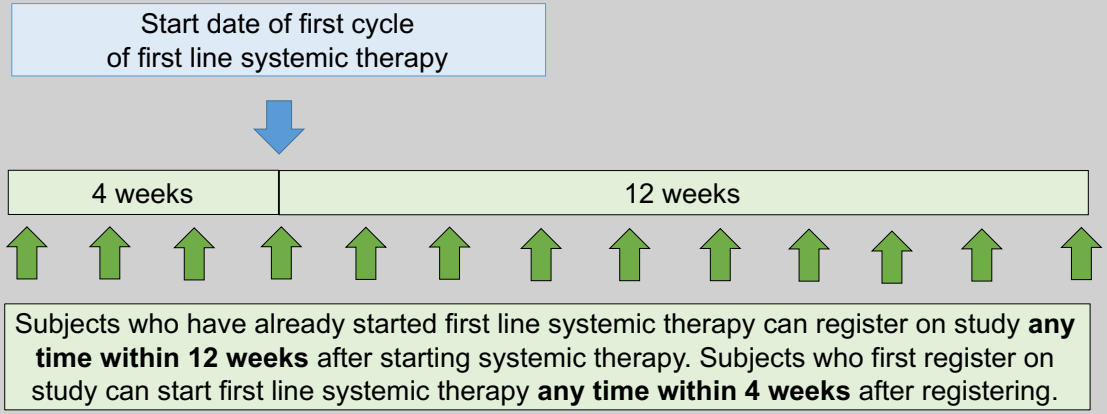
Eligibility Criteria

Patients can be registered for up to 4 weeks PRIOR to starting the first cycle of systemic therapy or any time within 12 weeks AFTER starting systemic therapy



Subjects who have already started first line systemic therapy can register on study **any time within 12 weeks** after starting systemic therapy. Subjects who first register on study can start first line systemic therapy **any time within 4 weeks** after registering.

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