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

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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 and prostate cancer. Compelling pre-clinical studies indicate that 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. In patients with advanced malignancies, symptoms related to progression of cancer and its treatments, as well the adverse effects of commonly used opioids, all contribute to impair the health-related quality of life (HRQoL).

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 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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Objective

Primary

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

Secondary

- HRQoL
- Pain levels and analgesic requirements
- Opioid adverse effects
- PFS and OS
- Chemotherapy discontinuation rate due to AEs
- Deaths attributable to chemotherapy

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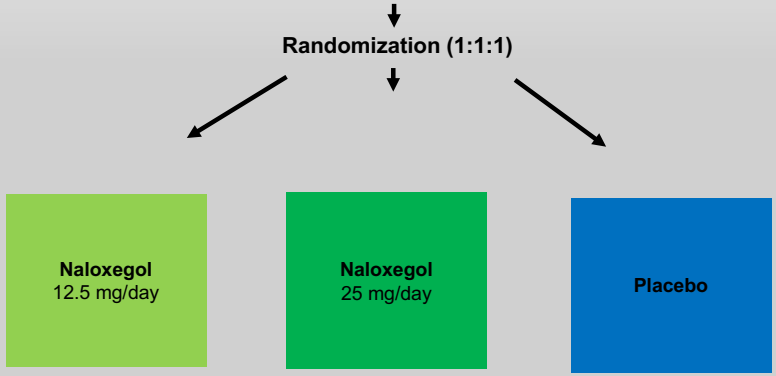
Study Schema

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. Expected accrual ~ 22 months

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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

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Eligibility Criteria

- Stage IIIB or IV non-small cell lung cancer (NSCLC).
- No known EGFR or EML4-ALK driver mutations.
- Any first-line systemic therapy ≤14 days of registration or planning to initiate ≤14 days after registration.
- +/- Pembrolizumab or +/- bevacizumab.
- Maintenance treatment OK.
- Prior adjuvant chemo/radiation, palliative radiation OK.•PS 0-2
- Opioid(s) used at some time in the 4 weeks < registration: see list of allowed and prohibited opioids
- Brain metastases: Eligible if EBRT or SBRT completed ≥ 7 days prior, or recovered from surgical resection.

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