A221504: A randomized, double-blind, placebo-controlled pilot study of an oral, selective peripheral opioid receptor antagonist in advanced non-small cell lung cancer (adenocarcinoma)

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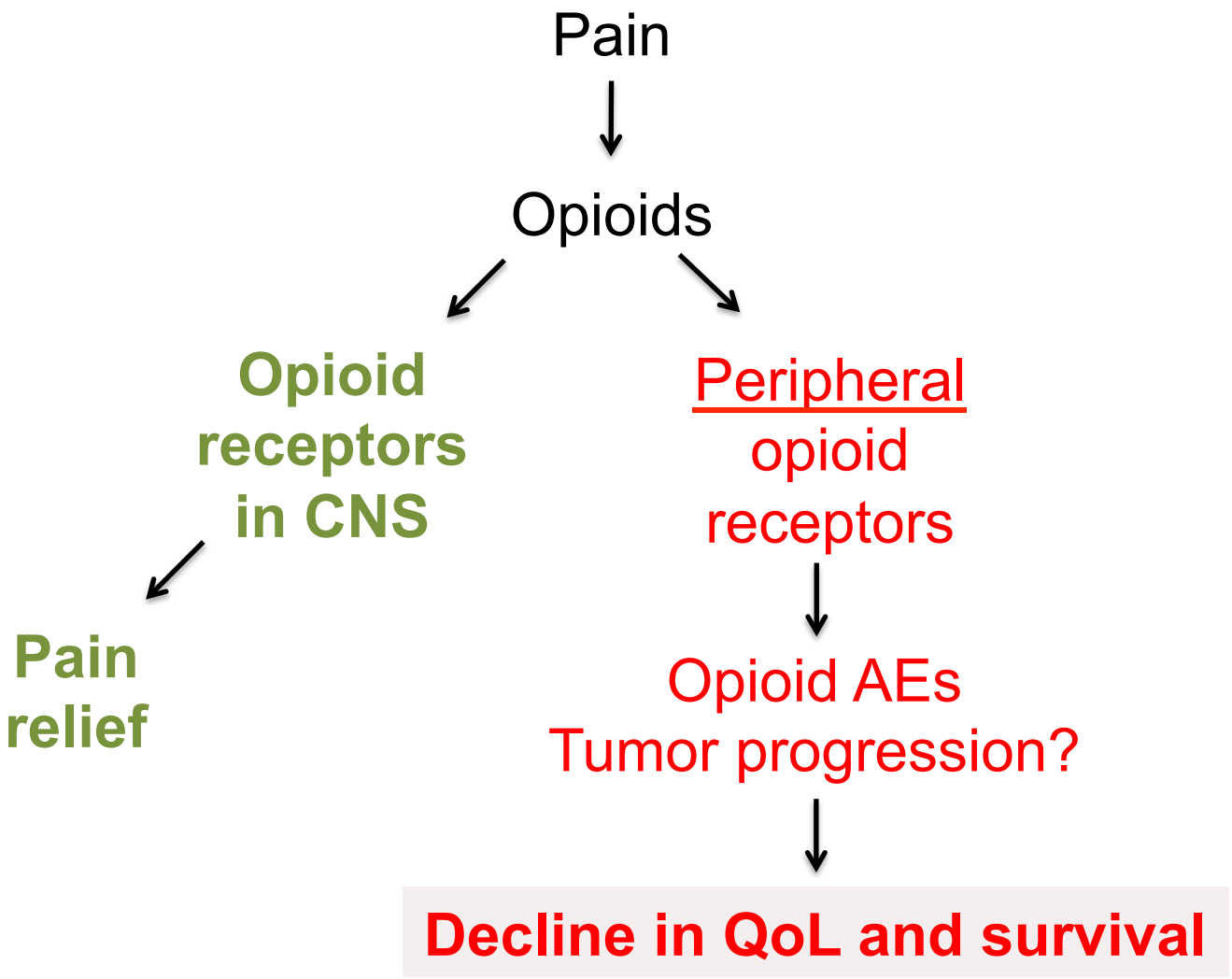
Background and Rationale



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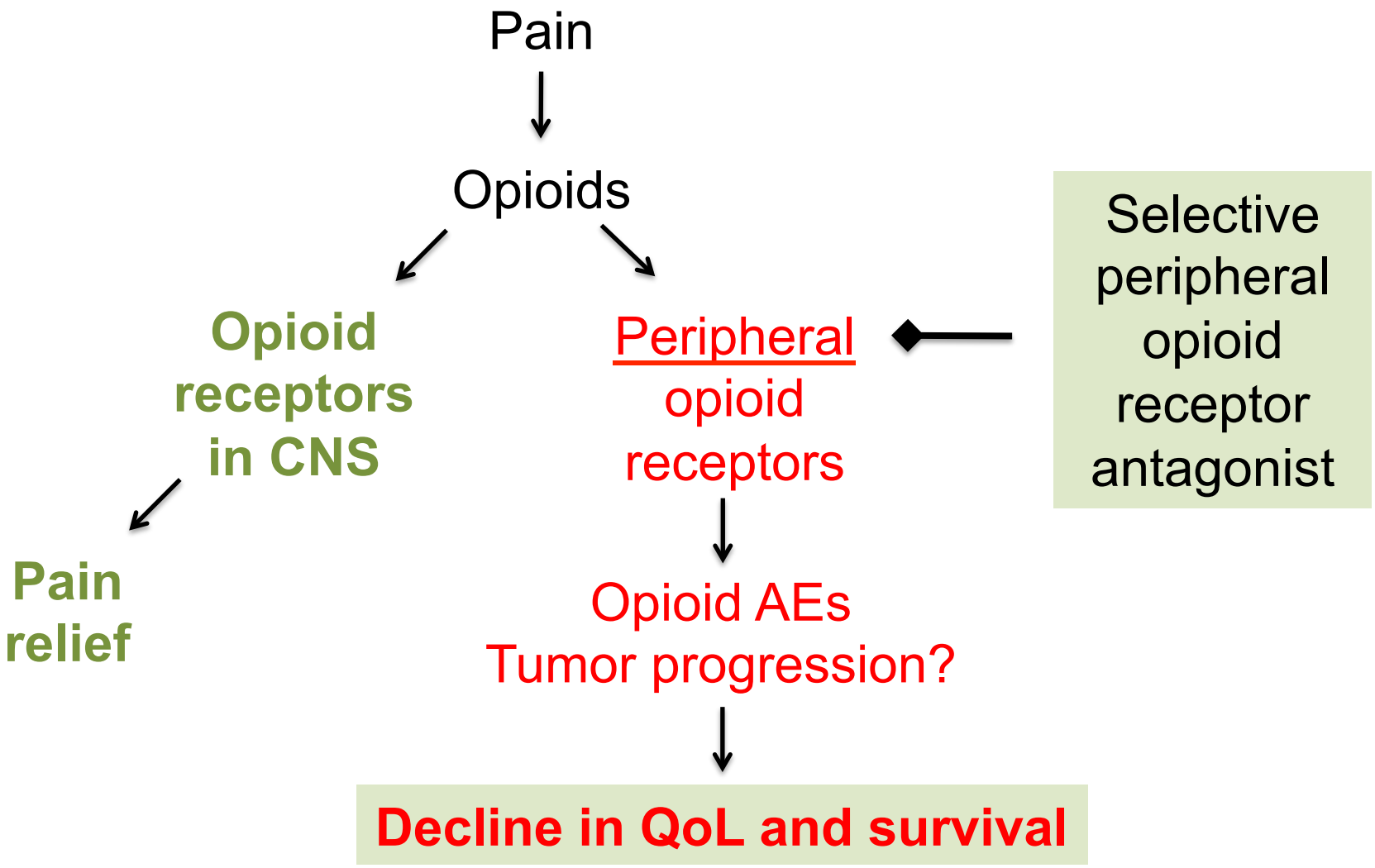

Naloxegol (Movantik®, AstraZeneca)

- Selective peripheral opioid receptor antagonist
- Orally bioavailable; once a day dosing
- Effective in relieving opioid-induced constipation
- Does not interfere with analgesic effect of opioids
- FDA-approved for long-term treatment of opioid-induced constipation in non-cancer patients
- No risk for dependency or abuse
- Not a controlled substance

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Objectives

Primary objective

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

Secondary objectives

- To explore whether patients randomized to naloxegol have less decline in HRQoL than pts randomized to placebo.
- To estimate the difference in pain levels and opioid/non-opioid analgesic requirements.
- To estimate the difference in the adverse peripheral effects of opioids (e.g. constipation, nausea/emesis, dry mouth and urinary retention).

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Objectives

- To explore whether there is a signal that naloxegol may be associated with longer PFS and OS.
- To evaluate the difference in discontinuation rate of chemotherapy due to AEs and deaths attributable to chemotherapy.

Correlative science objective

- To examine if MOR expression or activation is a prognostic marker in advanced NSCLC, and whether its expression and activation can be used to guide pain management.

Long term goal

- Obtain data to support/refute designing a phase III trial to determine whether naloxegol will improve survival.

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Eligibility Criteria

- Advanced (stage IIIB or IV) lung adenocarcinoma.
- No known EGFR or EML4-ALK driver mutations.
- Initiation of first-line chemotherapy with a platinum-pemetrexed-based regimen ≤14 days of registration or planning to initiate ≤14 days after registration.
- No prior systemic therapy for advanced NSCLC.
- Age ≥ 18 years. ECOG Performance Status 0-2. Not pregnant and not nursing. Expected survival > 3 months.
- Patients must have used opioid medication(s) for pain at some time in the 4 weeks prior to registration.
- No concurrently active second invasive malignancies except non-melanoma skin cancer.

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Eligibility Criteria

- No history of gastrointestinal obstruction or conditions that increase the risk of GI obstruction, perforation, bleeding or impairment of the GI wall. No abdominal surgery ≤ 60 days of registration. No acute GI conditions.
- No conditions that may compromise blood-brain barrier.
- No history of myocardial infarction ≤ 6 months.
- No severe hepatic impairment (Child-Pugh C), or acute liver disease.
- No known serious or severe hypersensitivity reaction to naloxegol or any of its excipients.
- No concurrent use of moderate/strong CYP3A4 inhibitors, strong CYP3A4 inducers, or other opioid antagonists or mixed agonists/antagonists. No past/current use of other peripheral opioid antagonists.

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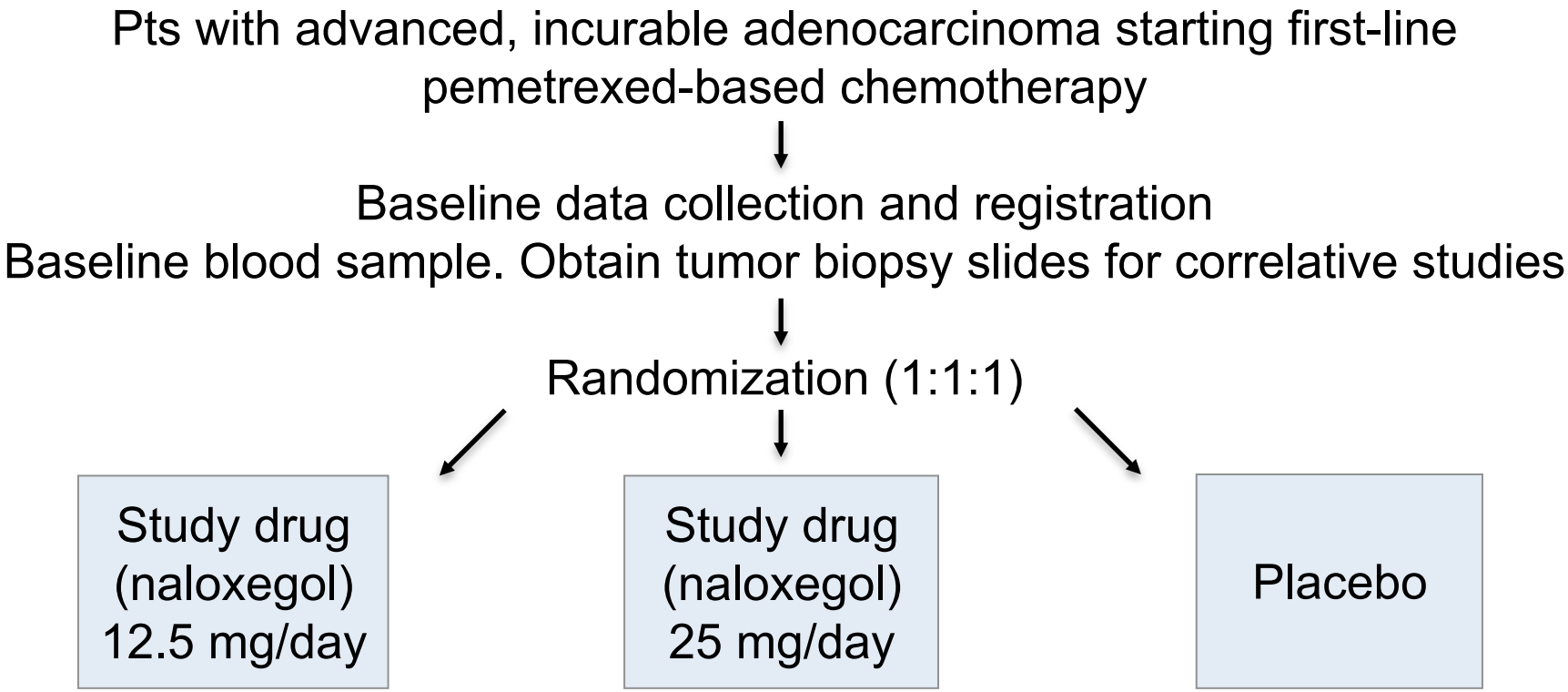
Schema



Data collection every 3-4 weeks for one year (at clinic visit or by mail).
Blood samples: once at 3-4 weeks and once at 6-8 weeks from initiation of study treatment

Study drug administered indefinitely. Discontinue for unacceptable AEs or withdrawal of consent.
Anti-cancer treatments (chemotherapy, radiation therapy), opioids/NSAIDs: physician discretion.

Correlative Studies

Objective

Examine if MOR expression/activation is a prognostic marker, and can be used to guide pain management.

Determine if the beneficial effect of naloxegol is limited to, or greater in, patients:

- Whose tumors demonstrate a higher level of MOR expression/activation
- With higher circulating levels of endogenous opioids, or
- Those requiring higher doses (≥5 mg/day average oral morphine equivalents [OME]) of opioids.

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Study Interest Survey of Alliance Community Investigators

Do you see this patient population in your practice?

Yes: 92%

Would you be interested in accruing patients onto this study at your site?

Yes: 78%

Approximately how many patients do you think you could accrue to this study per year?

117 patients per year

Expected accrual period for 204 patients: 20-22 months

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Questions, comments?

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Extra slides

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Eligibility Criteria

Required Initial Laboratory Values:

- Absolute neutrophil count (ANC) ≥ 1500/mm^3
- Platelet Count ≥ 100,000/mm^3
- Calc. Creatinine Clearance ≥ 60 mL/min*
- Total Bilirubin ≤ 1.2 x ULN**
- AST and ALT ≤ 2.5 x ULN
- EKG QT_c ≤ 500 msec
- Serum/urine HCG negative (not pregnant)

* Calculated using the Cockcroft-Gault formula
**Unless due to Gilbert's disease

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Treatment Strategy

Bottle 1 Dose	Bottle 2 Dose	Naloxegol Dose	Route	Day
12.5 mg Naloxegol	25 mg Placebo	12.5 mg	PO	Daily
12.5 mg Placebo	25 mg Naloxegol	25 mg	PO	Daily
12.5 mg Placebo	25 mg Placebo	0 mg	PO	Daily

All patients will take one pill from each of the 2 bottles, once every day

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Data collection schedule

	Baseline	Every 3 weeks x 1 year	Every 6 weeks x 1 year
Demographics	X		
H&P, smoking status, brain mets, EKG	X		
Stage	X		
Biopsy slides for correlative studies	X		
Blood samples for safety monitoring and for correlative studies	X	Once at 3 weeks	Once at 6 weeks
QOL (FACT-L)	X		X
PRO-CTCAE (dry mouth, vomiting, sweating); LASA (urinary retention)	X	Once at 3 weeks	X
Opioid-induced constipation rating scale	X	X	
Pain and analgesic use diary	X	X	
Adverse effects (routine clinical monitoring)		X*	
Anti-cancer treatment received	X	X	

For patients unable to continue coming for follow-up visits, data will be collected by mail.
After one year of treatment, pts will be followed for survival every 3 months.
* Routine AE monitoring will continue as long as patients remain on study drug.

Statistical Considerations

1:1:1 randomization to either of 2 doses of naloxegol or placebo.

n = 204 (68 patients per arm).

Assuming 10% ineligible: n = 184 (61 evaluable pts per arm).

Expected accrual: 9 -10 pts per month, completing accrual within 20 - 22 months.

Statistical Analysis for the Primary Endpoint:

Feasibility and safety will be evaluated by these criteria:

Rate of accrual ≥ 80% of expected (≥ 147 pts by 2 years),

≥ 80% of patients who remain alive at 6 months continuing on the study medication, and completing the HRQoL and other forms, for at least 6 months, and

Study continuing without meeting toxicity stopping criteria

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Statistical Considerations

Secondary objective:

Estimate the difference in HRQoL improvement at 6 months from baseline between the study treatment and placebo.

Observed improvement of ≥ 5.7 points in Trial Outcome Index (or ≥ 2 points in Lung Cancer Subscale of FACT-L) in one of the naloxegol arms vs placebo suggests a benefit in favor of naloxegol.

Sample size allows estimation with sufficient precision to detect a moderate effect size that falls within the published CMC range.

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