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## LUNG CANCER

## Preoperative PD1 checkpoint blockade and receptor activator of NFkB ligand (RANKL) inhibition in non-small cell lung cancer (NSCLC) (POPCORN).

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### WE RECOMMEND

**Background:** Preclinical studies indicate Receptor Activator of NF- $\kappa$ B Ligand (RANKL) blockade improves anti-tumor efficacy of immune checkpoint blockade (ICB). Clinical trials combining denosumab (anti-RANKL mAb) with ICB are underway in various cancers although the hypothesized mechanism of action of such combinations remains incomplete. RANKL and its receptor, RANK, are frequently expressed in NSCLC (tumor and immune cells). Denosumab demonstrated survival advantage over bisphosphonate in metastatic NSCLC (mNSCLC) to bone; a recent retrospective case series suggests a relationship between concurrent ICB and denosumab duration and survival in mNSCLC. Neoadjuvant nivolumab recently showed encouraging pathologic response rates in resectable NSCLC; neoadjuvant trials lend themselves to translational research. **Methods:** POPCORN is a multicenter phase 1b/2 study to determine the mechanism of action, activity and safety of neoadjuvant nivolumab plus denosumab versus nivolumab alone. 30 patients with resectable stage 1A (tumor > 2cm) – 3A NSCLC will be randomized 1:1 to two arms (Table). Exclusion criteria include uncontrolled autoimmune disease, steroid contraindications, and unhealed dental disease. Tumor tissue at baseline, surgery and relapse, and peripheral blood at various timepoints (including on-therapy) will be collected. The primary endpoint is to define pharmacodynamic correlates of the two arms through investigations including T-cell receptor clonality, RNA/transcription profile changes (tumor and peripheral blood), and expression of tumor/immune markers of interest via multiplex immunohistochemistry, compared between groups. Secondary endpoints include pathologic response rates, toxicity, R0 resection, and PFS/OS (exploratory). Statistical analysis will be primarily descriptive on the intention-to-treat population. The trial is sponsored by Metro North Hospital and Health Service (Queensland, Australia) with funding from AMGEN, Inc. [Clinical trial information: ACTRN12618001121257](#).

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By Alice Goodman, The ASCO Post, 2019
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- Atezolizumab (Tecentriq) for Bladder Cancer and NSCLC (online only)  
The Medical Letter, 2017
- Pembrolizumab (Keytruda) for First-Line Treatment of Metastatic NSCLC  
The Medical Letter, 2017



Arm	Drug	Week 1 (Day 1)	Week 3 (Day 15)	Week 5 (Day 29)
Arm 1	Nivolumab (3 mg/kg i.v)	X	X	Surgery
Arm 2	Nivolumab (3 mg/kg i.v)	X	X	Surgery
	Denosumab (120 mg s.c)	X	X	

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