(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 September 2022 (22.09.2022)

WIPO | PCT

(10) International Publication Number
WO 2022/197767 A1

(51) International Patent Classification:
*A61P 35/00* (2006.01) *A61K 31/137* (2006.01)
*A61K 31/135* (2006.01)

(21) International Application Number:
PCT/US2022/020497

(22) International Filing Date:
16 March 2022 (16.03.2022)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
63/162,291 17 March 2021 (17.03.2021) US

(71) Applicants: **MEMORIAL SLOAN-KETTERING CANCER CENTER** [US/US]; 1275 York Avenue, New York, New York 10065 (US). **MEMORIAL HOSPITAL FOR CANCER AND ALLIED DISEASES** [US/US]; 1275 York Avenue, New York, New York 10065 (US). **SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH** [US/US]; 1275 York Avenue, New York, New York 10065 (US).

(72) Inventors: **MINCER, Joshua**; c/o Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, New York 10065 (US). **FISCHER, Gregory**; c/o Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, New York 10065 (US). **MCCORMICK, Patrick**; c/o Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, New York 10065 (US).

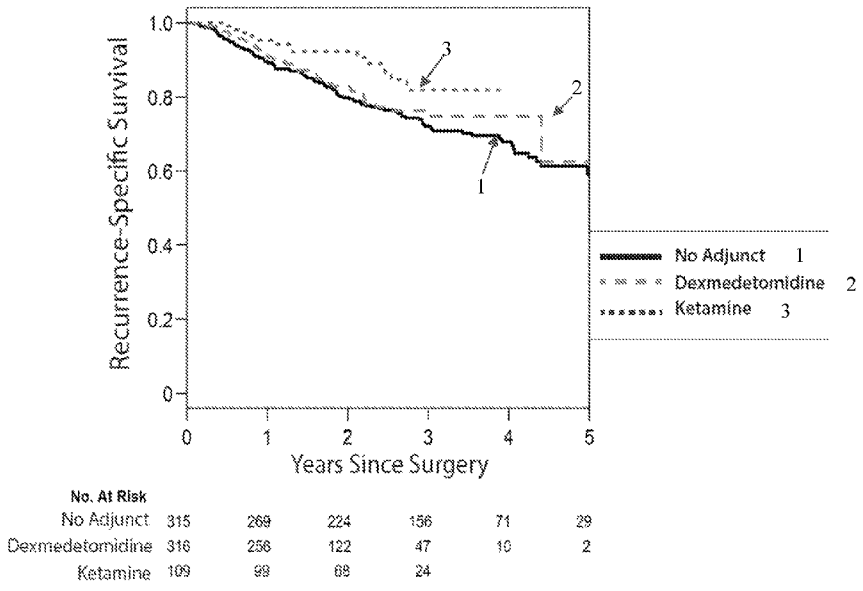
(74) Agent: **EWING, James F.** et al.; FOLEY & LARDNER LLP, 3000 K Street NW, Suite 600, Washington, District of Columbia 20007 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JM, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ,

(54) Title: METHODS FOR IMPROVING SURVIVAL IN LUNG CANCER PATIENTS VIA KETAMINE ONCOPROTECTION

FIG. 1A




(57) Abstract: The present disclosure provides methods for improving survival in lung cancer patients undergoing tumor resection surgery using ketamine.

[Continued on next page]

WO 2022/197767 A1

UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

**Published:**

— *with international search report (Art. 21(3))*

# METHODS FOR IMPROVING SURVIVAL IN LUNG CANCER PATIENTS VIA KETAMINE ONCOPROTECTION

## CROSS-REFERENCE TO RELATED APPLICATIONS

**[0001]** This application claims the benefit of and priority to U.S. Provisional Patent Application No. 63/162,291, filed March 17, 2021, the entire contents of which are incorporated herein by reference.

## TECHNICAL FIELD

**[0002]** The present technology relates generally to methods for improving survival in lung cancer patients undergoing tumor resection surgery comprising administering to the subject an effective amount of ketamine.

## STATEMENT OF GOVERNMENT SUPPORT

**[0003]** This invention was made with government support under grant number CA008748 awarded by the National Cancer Institute. The government has certain rights in the invention.

## BACKGROUND

**[0004]** The following description of the background of the present technology is provided simply as an aid in understanding the present technology and is not admitted to describe or constitute prior art to the present technology.

**[0005]** Ketamine is a drug used for the induction and maintenance of general anesthesia, for the treatment of postoperative and posttraumatic acute pain, and more recently, for the reduction of postoperative opioid requirements. The main mechanism of action of ketamine is the antagonization of N-methyl-D-aspartate (NMDA) receptors that are associated with central sensitization. In the pathogenesis of chronic pain and particularly in neuropathic pain, an important role is played by the activation of NMDA receptors.

## SUMMARY OF THE PRESENT TECHNOLOGY

**[0006]** In one aspect, the present disclosure provides a method for prolonging survival of a lung cancer patient undergoing tumor resection surgery comprising administering to the cancer patient an effective amount of ketamine during the tumor resection surgery. The effective amount of ketamine may be administered as a series of bolus doses or as a

continuous infusion during the tumor resection surgery. In some embodiments, the ketamine is administered intravenously. The effective amount of ketamine may be administered intraoperatively, preoperatively, and/or postoperatively.

**[0007]** Additionally or alternatively, in some embodiments, the ketamine is infused at a rate of 0.04 mg/kg/hr-2.5 mg/kg/hr. In some embodiments of the methods disclosed herein, the ketamine is infused at a rate of about 0.04 mg/kg/hr, about 0.05 mg/kg/hr, about 0.06 mg/kg/hr, about 0.07 mg/kg/hr, about 0.08 mg/kg/hr, about 0.09 mg/kg/hr, about 0.1 mg/kg/hr, about 0.2 mg/kg/hr, about 0.3 mg/kg/hr, about 0.4 mg/kg/hr, about 0.5 mg/kg/hr, about 0.6 mg/kg/hr, about 0.7 mg/kg/hr, about 0.8 mg/kg/hr, about 0.9 mg/kg/hr, about 1.0 mg/kg/hr, about 1.1 mg/kg/hr, about 1.2 mg/kg/hr, about 1.3 mg/kg/hr, about 1.4 mg/kg/hr, about 1.5 mg/kg/hr, about 1.6 mg/kg/hr, about 1.7 mg/kg/hr, about 1.8 mg/kg/hr, about 1.9 mg/kg/hr, about 2.0 mg/kg/hr, about 2.1 mg/kg/hr, about 2.2 mg/kg/hr, about 2.3 mg/kg/hr, about 2.4 mg/kg/hr, or about 2.5 mg/kg/hr.

**[0008]** Additionally or alternatively, in some embodiments, the ketamine is administered as a bolus of 0.5 mg/kg -4.5 mg/kg. In some embodiments of the methods disclosed herein, the ketamine is administered as a bolus of about 0.04 mg/kg, about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg, about 0.08 mg/kg, about 0.09 mg/kg, about 0.1 mg/kg, about 0.2 mg/kg, about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, about 0.8 mg/kg, about 0.9 mg/kg, about 1.0 mg/kg, about 1.1 mg/kg, about 1.2 mg/kg, about 1.3 mg/kg, about 1.4 mg/kg, about 1.5 mg/kg, about 1.6 mg/kg, about 1.7 mg/kg, about 1.8 mg/kg, about 1.9 mg/kg, about 2.0 mg/kg, about 2.1 mg/kg, about 2.2 mg/kg, about 2.3 mg/kg, about 2.4 mg/kg, about 2.5 mg/kg, about 2.6 mg/kg, about 2.7 mg/kg, about 2.8 mg/kg, about 2.9 mg/kg, about 3.0 mg/kg, about 3.1 mg/kg, about 3.2 mg/kg, about 3.3 mg/kg, about 3.4 mg/kg, about 3.5 mg/kg, about 3.6 mg/kg, about 3.7 mg/kg, about 3.8 mg/kg, about 3.9 mg/kg, about 4.0 mg/kg, about 4.1 mg/kg, about 4.2 mg/kg, about 4.3 mg/kg, about 4.4 mg/kg, or about 4.5 mg/kg.

**[0009]** Additionally or alternatively, in some embodiments, the ketamine is administered intramuscularly at a dose of about 4-13 mg/kg. In certain embodiments of the methods disclosed herein, the ketamine is administered intramuscularly at a dose of 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 11 mg/kg, 12 mg/kg, or 13 mg/kg. Additionally or alternatively, in some embodiments, the ketamine is administered orally at a dose of about 6-10 mg/kg. In certain embodiments of the methods disclosed herein, the

ketamine is administered orally at a dose of 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, or 10 mg/kg.

**[0010]** Additionally or alternatively, in some embodiments, the methods of the present technology further comprise administering to the cancer patient an effective amount of an intraoperative opioid analgesic. The intraoperative opioid analgesic may be fentanyl, hydromorphone, morphine, oxycodone, hydrocodone, codeine, meperidine, remifentanil, or sufentanil. The effective amount of the intraoperative opioid analgesic may range from about 1 MME to about 200 MMEs. In certain embodiments, the effective amount of the intraoperative opioid analgesic is about 1 MME to about 20 MMEs, about 20 MMEs to about 45 MMEs, or about 45 MMEs to about 200 MMEs. In some embodiments, the effective amount of the intraoperative opioid analgesic is about 1 MME, about 2 MMEs, about 3 MMEs, about 4 MMEs, about 5 MMEs, about 6 MMEs, about 7 MMEs, about 8 MMEs, about 9 MMEs, about 10 MMEs, about 11 MMEs, about 12 MMEs, about 13 MMEs, about 14 MMEs, about 15 MMEs, about 16 MMEs, about 17 MMEs, about 18 MMEs, about 19 MMEs, about 20 MMEs, about 21 MMEs, about 22 MMEs, about 23 MMEs, about 24 MMEs, about 25 MMEs, about 26 MMEs, about 27 MMEs, about 28 MMEs, about 29 MMEs, about 30 MMEs, about 31 MMEs, about 32 MMEs, about 33 MMEs, about 34 MMEs, about 35 MMEs, about 36 MMEs, about 37 MMEs, about 38 MMEs, about 39 MMEs, about 40-45 MMEs, about 45-50 MMEs, about 50-55 MMEs, about 55-60 MMEs, about 60-65 MMEs, about 65-70 MMEs, about 70-75 MMEs, about 75-80 MMEs, about 80-85 MMEs, about 85-90 MMEs, about 90-95 MMEs, about 95-100 MMEs, about 100-110 MMEs, about 110-120 MMEs, about 120-130 MMEs, about 130-140 MMEs, about 140-150 MMEs, about 150-160 MMEs, about 160-170 MMEs, about 170-180 MMEs, about 180-190 MMEs, or about 190-200 MMEs. Additionally or alternatively, in some embodiments, the effective amount of the intraoperative opioid analgesic is administered as a series of bolus doses or as a continuous infusion during the tumor resection surgery. In certain embodiments, the effective amount of the intraoperative opioid analgesic is administered to the cancer patient prior to incision. Additionally or alternatively, in some embodiments, the effective amount of the intraoperative opioid analgesic is administered intravenously.

**[0011]** Additionally or alternatively, in some embodiments, the method further comprises administering to the cancer patient an effective amount of a local anesthetic solution that

comprises one or more of lidocaine, mepivacaine, prilocaine, bupivacaine, etidocaine, ropivacaine, levobupivacaine, cocaine, procaine, tetracaine, chloroprocaine, or benzocaine, and optionally an opioid. In some embodiments, the methods of the present technology further comprise administering to the cancer patient an effective amount of a local anesthetic solution via an epidural catheter before, during and/or after the tumor resection surgery. The effective amount of the local anesthetic solution may range from about 0.05%-4% local anesthetic solution in a volume of 1-10 ml per hour when administered via an epidural catheter. In some embodiments, the effective amount of the local anesthetic solution is about 0.05 %, about 0.06 %, about 0.07 %, about 0.08 %, about 0.09 %, about 0.1 %, about 0.15 %, about 0.2 %, about 0.25 %, about 0.3 %, about 0.35 %, about 0.4 %, about 0.45 %, about 0.5 %, about 0.55 %, about 0.6 %, about 0.65 %, about 0.7 %, about 0.75 %, about 0.8 %, about 0.85 %, about 0.9 %, about 0.95 %, about 1.0 %, about 1.1 %, about 1.2 %, about 1.3 %, about 1.4 %, about 1.5 %, about 1.6 %, about 1.7 %, about 1.8 %, about 1.9 %, about 2.0 %, about 2.1 %, about 2.2 %, about 2.3 %, about 2.4 %, about 2.5 %, about 2.6 %, about 2.7 %, about 2.8 %, about 2.9 %, about 3.0 %, about 3.1 %, about 3.2 %, about 3.3 %, about 3.4 %, about 3.5 %, about 3.6 %, about 3.7 %, about 3.8 %, about 3.9 %, or about 4.0 % local anesthetic solution in a volume of about 1 ml per hour, about 1.5 ml per hour, about 2 ml per hour, about 2.5 ml per hour, about 3 ml per hour, about 3.5 ml per hour, about 4 ml per hour, about 4.5 ml per hour, about 5 ml per hour, about 5.5 ml per hour, about 6 ml per hour, about 6.5 ml per hour, about 7 ml per hour, about 7.5 ml per hour, about 8 ml per hour, about 8.5 ml per hour, about 9 ml per hour, about 9.5 ml per hour, or about 10 ml per hour when administered via an epidural catheter. Additionally or alternatively, in some embodiments, the effective amount of the local anesthetic solution is administered as a single injection, a series of bolus doses or as a continuous infusion during the tumor resection surgery. Examples of suitable local anesthetics include, but are not limited to, lidocaine, mepivacaine, prilocaine, bupivacaine, etidocaine, ropivacaine, levobupivacaine, cocaine, procaine, tetracaine, chloroprocaine, and benzocaine.

**[0012]** In other embodiments, the effective amount of the local anesthetic solution may be administered before, during and/or after the tumor resection surgery using any regional anesthesia technique directed at nerves innervating the thorax and chest wall (*e.g.*, via serratus plane nerve block, intercostal nerve block, or paravertebral block). The effective amount of the local anesthetic solution may range from about 0.05%-4% local anesthetic

solution in a volume of 10-40 ml when administered using any regional anesthesia technique directed at nerves innervating the thorax and chest wall (*e.g.*, via serratus plane nerve block, intercostal nerve block, or paravertebral block). In some embodiments, the effective amount of the local anesthetic solution is about 0.05 %, about 0.06 %, about 0.07 %, about 0.08 %, about 0.09 %, about 0.1 %, about 0.15 %, about 0.2 %, about 0.25 %, about 0.3 %, about 0.35 %, about 0.4 %, about 0.45 %, about 0.5 %, about 0.55 %, about 0.6 %, about 0.65 %, about 0.7 %, about 0.75 %, about 0.8 %, about 0.85 %, about 0.9 %, about 0.95 %, about 1.0 %, about 1.1 %, about 1.2 %, about 1.3 %, about 1.4 %, about 1.5 %, about 1.6 %, about 1.7 %, about 1.8 %, about 1.9 %, about 2.0 %, about 2.1 %, about 2.2 %, about 2.3 %, about 2.4 %, about 2.5 %, about 2.6 %, about 2.7 %, about 2.8 %, about 2.9 %, about 3.0 %, about 3.1 %, about 3.2 %, about 3.3 %, about 3.4 %, about 3.5 %, about 3.6 %, about 3.7 %, about 3.8 %, about 3.9 %, or about 4.0 % local anesthetic solution in a volume of about 10 ml, about 12.5 ml, about 15 ml, about 17.5 ml, about 20 ml, about 22.5 ml, about 25 ml, about 27.5 ml, about 30 ml, about 32.5 ml, about 35 ml, about 37.5 ml, or about 40 ml when administered using any regional anesthesia technique directed at nerves innervating the thorax and chest wall (*e.g.*, via serratus plane nerve block, intercostal nerve block, or paravertebral block). Examples of suitable local anesthetics include, but are not limited to, lidocaine, mepivacaine, prilocaine, bupivacaine, etidocaine, ropivacaine, levobupivacaine, cocaine, procaine, tetracaine, chloroprocaine, and benzocaine.

**[0013]** Additionally or alternatively, in certain embodiments, the local anesthetic solution may further comprise an opioid (*e.g.*, fentanyl, hydromorphone, morphine, oxycodone, hydrocodone, codeine, meperidine, remifentanil, or sufentanil). In some embodiments, the local anesthetic solution may comprise 0.5 mcg/ml-50 mcg/ml opioid. In certain embodiments, the local anesthetic solution may comprise about 0.5 mcg/ml, about 0.6 mcg/ml, about 0.7 mcg/ml, about 0.8 mcg/ml, about 0.9 mcg/ml, about 1.0 mcg/ml, about 1.5 mcg/ml, about 2.0 mcg/ml, about 2.5 mcg/ml, about 3.0 mcg/ml, about 3.5 mcg/ml, about 4.0 mcg/ml, about 4.5 mcg/ml, about 5.0 mcg/ml, about 5.5 mcg/ml, about 6.0 mcg/ml, about 6.5 mcg/ml, about 7.0 mcg/ml, about 7.5 mcg/ml, about 8.0 mcg/ml, about 8.5 mcg/ml, about 9.0 mcg/ml, about 10 mcg/ml, about 15 mcg/ml, about 20 mcg/ml, about 25 mcg/ml, about 30 mcg/ml, about 35 mcg/ml, about 40 mcg/ml, about 45 mcg/ml, or about 50 mcg/ml.

**[0014]** Additionally or alternatively, in some embodiments, the methods of the present technology further comprise administering to the cancer patient an effective amount of a post-operative opioid analgesic after the tumor resection surgery. Examples of post-operative opioid analgesics include, but are not limited to, fentanyl, hydromorphone, morphine, oxycodone, hydrocodone, codeine, meperidine, remifentanil, or sufentanil. In some embodiments, the post-operative opioid analgesic and the intraoperative opioid analgesic are the same opioid analgesic or different opioid analgesics. In other embodiments, the effective amount of the post-operative opioid analgesic and the effective amount of the intraoperative opioid analgesic are the same or different. Additionally or alternatively, in some embodiments, the effective amount of the post-operative opioid analgesic is administered to the cancer patient as a bolus of about 0.005 mg to about 100 mg. In some embodiments, the effective amount of the post-operative opioid analgesic is administered to the cancer patient as a bolus of about 0.005 mg, about 0.006 mg, about 0.007 mg, about 0.008 mg, about 0.009 mg, about 0.01 mg, about 0.02 mg, about 0.03 mg, about 0.04 mg, about 0.05 mg, about 0.06 mg, about 0.07 mg, about 0.08 mg, about 0.09 mg, about 0.1 mg, about 0.2 mg, about 0.3 mg, about 0.4 mg, about 0.5 mg, about 0.6 mg, about 0.7 mg, about 0.8 mg, about 0.9 mg, about 1-5 mg, about 5-10 mg, about 1-5 mg, about 5-10 mg, about 1-5 mg, about 5-10 mg, about 1-5 mg, about 5-10 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 25-30 mg, about 30-35 mg, about 35-40 mg, about 40-45 mg, about 45-50 mg, about 50-55 mg, about 55-60 mg, about 60-65 mg, about 65-70 mg, about 70-75 mg, about 75-80 mg, about 80-85 mg, about 85-90 mg, about 90-95 mg, or about 95-100 mg. In other embodiments, the effective amount of the post-operative opioid analgesic may be continuously delivered to the cancer patient at a per hour rate of about 0.01 mg/hr to about 10 mg/hr. In certain embodiments, the effective amount of the post-operative opioid analgesic is continuously delivered to the cancer patient at a per hour rate of about 0.01 mg/hr, about 0.02 mg/hr, about 0.03 mg/hr, about 0.04 mg/hr, about 0.05 mg/hr, about 0.06 mg/hr, about 0.07 mg/hr, about 0.08 mg/hr, about 0.09 mg/hr, about 0.1 mg/hr, about 0.2 mg/hr, about 0.3 mg/hr, about 0.4 mg/hr, about 0.5 mg/hr, about 0.6 mg/hr, about 0.7 mg/hr, about 0.8 mg/hr, about 0.9 mg/hr, about 1 mg/hr, about 1.5 mg/hr, about 2 mg/hr, about 2.5 mg/hr, about 3 mg/hr, about 3.5 mg/hr, about 4 mg/hr, about 4.5 mg/hr, about 5 mg/hr, about 5.5 mg/hr, about 6 mg/hr, about 6.5 mg/hr, about 7 mg/hr, about 7.5 mg/hr, about 8 mg/hr, about 8.5 mg/hr, about 9 mg/hr, about 9.5 mg/hr, or about 10 mg/hr.

Additionally or alternatively, in some embodiments, the effective amount of the post-operative opioid analgesic is administered intravenously, orally, or transdermally.

**[0015]** In other embodiments, the methods of the present technology further comprise administering to the cancer patient an effective amount of an opioid-free post-operative analgesic after the tumor resection surgery. Examples of suitable opioid-free post-operative analgesics include, but are not limited to, lidocaine, mepivacaine, prilocaine, bupivacaine, etidocaine, ropivacaine, levobupivacaine, cocaine, procaine, tetracaine, chloroprocaine, and benzocaine. In some embodiments, the opioid-free post-operative analgesic and the opioid-free intraoperative analgesic are the same analgesic or different analgesics. In other embodiments, the effective amount of the opioid-free post-operative analgesic and the effective amount of the opioid-free intraoperative analgesic are the same or different.

**[0016]** In any and all embodiments of the methods disclosed herein, the cancer patient exhibits stage I, stage II or stage III lung cancer. Additionally or alternatively, in some embodiments, the cancer patient has been diagnosed with lung adenocarcinoma (LUAD). The histologic subtype of the lung adenocarcinoma may be lepidic, acinar, papillary, micropapillary, solid or unknown.

**[0017]** In any of the preceding embodiments of the methods disclosed herein, the cancer patient has received an adjuvant therapy. The adjuvant therapy may be chemotherapy, lobectomy, radiation therapy or chemoradiation therapy. Additionally or alternatively, in some embodiments of the methods disclosed herein, the patient is human.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0018]** **FIGs. 1A-1C** show association of intraoperative opioid dose and analgesic adjuncts with survival and recurrence in lung adenocarcinoma patients. **FIG. 1A** shows five-year Kaplan-Meier curves for recurrence-specific survival for lung adenocarcinoma patients who received no adjunct, ketamine, and dexmedetomidine intraoperatively. **FIG. 1B** shows five-year predicted curve for overall survival with increasing intraoperative MME dose. OS, overall survival; RSS, recurrence specific survival; MME, oral morphine milligram equivalents. **FIG. 1C** shows predicted five-year curves for recurrence-specific survival for lung adenocarcinoma patients who received different intraoperative doses of opioids and either no adjunct, or ketamine adjunct therapy, or dexmedetomidine adjunct therapy.

**[0019] FIG. 2** shows CONSORT diagram demonstrating exclusion criteria for the patient cohort. MSK-IMPACT: Memorial Sloan Kettering–Integrated Mutation Profiling of Actionable Cancer Targets.

**[0020] FIG. 3** shows multivariable analysis for all intraoperative analgesics and clinicopathologic factors significantly associated with overall survival and recurrence-specific survival on univariable analysis. Red error bars (annotated by *) indicate significant difference compared to reference group for each variable.

**[0021] FIG. 4** shows summary of clinical and intraoperative characteristics by analgesic adjunct group. Data are median (interquartile range) or no. (%). MME, oral morphine milligram equivalents; BMI, body mass index; EBL, estimate blood loss; MAP, mean arterial pressure; HR, heart rate.

**[0022] FIG. 5** shows univariable Cox model of intraoperative analgesics and clinicopathologic factors for recurrence specific survival and overall survival, stratified by pathologic stage in lung adenocarcinoma patients. EvW score, Elixhauser-van Walraven score; HR, Hazard Ratio; CI, Confidence Interval; MME, oral milligram morphine equivalents; Pneumo/bilobe, pneumonectomy/bilobectomy.

**[0023] FIGs. 6A-6B** show analysis of total intraoperative MME in terms of specific opioids received. **FIG. 6A** shows breakdown by patient of specific opioid type (fentanyl, hydromorphone, morphine) as a contribution to total intraoperative MME. **FIG. 6B** shows cumulative percentage of fentanyl fraction of total intraoperative MME (fentanyl dose divided by total dose).

## DETAILED DESCRIPTION

**[0024]** It is to be appreciated that certain aspects, modes, embodiments, variations and features of the present methods are described below in various levels of detail in order to provide a substantial understanding of the present technology. It is to be understood that the present disclosure is not limited to particular uses, methods, reagents, compounds, compositions or biological systems, which can, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

**[0025]** In practicing the present methods, many conventional techniques in molecular biology, protein biochemistry, cell biology, microbiology and recombinant DNA are used. *See*, *e.g.*, Sambrook and Russell eds. (2001) *Molecular Cloning: A Laboratory Manual*, 3rd edition; the series Ausubel *et al.*, eds. (2007) *Current Protocols in Molecular Biology*; the series *Methods in Enzymology* (Academic Press, Inc., N.Y.); MacPherson *et al.*, (1991) *PCR 1: A Practical Approach* (IRL Press at Oxford University Press); MacPherson *et al.*, (1995) *PCR 2: A Practical Approach*; Harlow and Lane eds. (1999) *Antibodies, A Laboratory Manual*; Freshney (2005) *Culture of Animal Cells: A Manual of Basic Technique*, 5th edition; Gait ed. (1984) *Oligonucleotide Synthesis*; U.S. Patent No. 4,683,195; Hames and Higgins eds. (1984) *Nucleic Acid Hybridization*; Anderson (1999) *Nucleic Acid Hybridization*; Hames and Higgins eds. (1984) *Transcription and Translation; Immobilized Cells and Enzymes* (IRL Press (1986)); Perbal (1984) *A Practical Guide to Molecular Cloning*; Miller and Calos eds. (1987) *Gene Transfer Vectors for Mammalian Cells* (Cold Spring Harbor Laboratory); Makrides ed. (2003) *Gene Transfer and Expression in Mammalian Cells*; Mayer and Walker eds. (1987) *Immunochemical Methods in Cell and Molecular Biology* (Academic Press, London); and Herzenberg *et al.*, eds (1996) *Weir's Handbook of Experimental Immunology*.

**[0026]** Diverse cancers exhibit significant variations in their response to therapeutic interventions (Kluger *et al., Clin Cancer Res* 2017 (23) (15) 4270-4279; Topalin *et al.*, *JAMA Oncol.* 2019;5(10):1411-1420), which may be attributable at least in part to their distinct molecular pathologies. For instance, non-small cell lung carcinoma has a high tumor mutational burden (TMB) and a high frequency of p53 mutations, whereas renal cell carcinoma (RCC) on the other hand shows a low TMB and is characterized by 3p loss & VHL mutation.

**[0027]** The impact of intraoperative anesthetic adjuncts such as ketamine, and dexmedetomidine on survival and recurrence in operative lung adenocarcinoma patients is unknown. The present disclosure demonstrates that the administration of ketamine to lung cancer patients undergoing tumor resection surgery was significantly associated with improved RSS compared to patients who received no adjunct therapy. As demonstrated in the multivariable analysis of **FIG. 3**, when all else is kept equal (two patients: with same age, VWscore, Procedure, histology and pathologic stage, and the same MME [could be both 0, could be both 100 units]), the patient with Ketamine has 66% lower hazard of

recurrence compared to the patient with no adjunct (HR=0.55, 95% CI 0.24 – 0.80, p=0.007).

**Definitions**

**[0028]** Unless defined otherwise, all technical and scientific terms used herein generally have the same meaning as commonly understood by one of ordinary skill in the art to which this technology belongs. As used in this specification and the appended claims, the singular forms "a", "an" and "the" include plural referents unless the content clearly dictates otherwise. For example, reference to "a cell" includes a combination of two or more cells, and the like. Generally, the nomenclature used herein and the laboratory procedures in cell culture, molecular genetics, organic chemistry, analytical chemistry and nucleic acid chemistry and hybridization described below are those well-known and commonly employed in the art.

**[0029]** As used herein, the term "about" in reference to a number is generally taken to include numbers that fall within a range of 1%, 5%, or 10% in either direction (greater than or less than) of the number unless otherwise stated or otherwise evident from the context (except where such number would be less than 0% or exceed 100% of a possible value).

**[0030]** As used herein, the "administration" of an agent or drug to a subject includes any route of introducing or delivering to a subject a compound to perform its intended function. Administration can be carried out by any suitable route, including but not limited to, orally, intranasally, parenterally (intravenously, intramuscularly, intraperitoneally, or subcutaneously), rectally, intrathecally, intratumorally or topically. Administration includes self-administration and the administration by another.

**[0031]** The terms "cancer" or "tumor" are used interchangeably and refer to the presence of cells possessing characteristics typical of cancer-causing cells, such as uncontrolled proliferation, immortality, metastatic potential, rapid growth and proliferation rate, and certain characteristic morphological features. Cancer cells are often in the form of a tumor, but such cells can exist alone within an animal, or can be a non-tumorigenic cancer cell. As used herein, the term "cancer" includes premalignant, as well as malignant cancers.

**[0032]** As used herein, a "control" is an alternative sample used in an experiment for comparison purpose. A control can be "positive" or "negative." For example, where the purpose of the experiment is to determine a correlation of the efficacy of a therapeutic agent

for the treatment for a particular type of disease, a positive control (a compound or composition known to exhibit the desired therapeutic effect) and a negative control (a subject or a sample that does not receive the therapy or receives a placebo) are typically employed.

**[0033]** As used herein, the term "effective amount" refers to a quantity sufficient to achieve a desired therapeutic and/or prophylactic effect, *e.g.*, an amount which results in the prevention of, or a decrease in a disease or condition described herein or one or more signs or symptoms associated with a disease or condition described herein. In the context of therapeutic or prophylactic applications, the amount of a composition administered to the subject will vary depending on the composition, the degree, type, and severity of the disease and on the characteristics of the individual, such as general health, age, sex, body weight and tolerance to drugs. The skilled artisan will be able to determine appropriate dosages depending on these and other factors. The compositions can also be administered in combination with one or more additional therapeutic compounds. In the methods described herein, the therapeutic compositions may be administered to a subject having one or more signs or symptoms of a disease or condition described herein. As used herein, a "therapeutically effective amount" of a composition refers to composition levels in which the physiological effects of a disease or condition are ameliorated or eliminated. A therapeutically effective amount can be given in one or more administrations.

**[0034]** As used herein, the term "overall survival" or "OS" means the observed length of life from the start of treatment to death or the date of last contact.

**[0035]** As used herein, the term "perioperative" refers to the time period of a patient's surgical procedure. It commonly includes ward admission, anesthesia, surgery, and recovery. The perioperative period is characterized by a sequence including the time preceding an operation when a patient is being prepared for surgery ("the preoperative period"), followed by the time spent in surgery ("the intraoperative period"), and by the time following an operation when the patient is closely monitored for complications while recovering from the effects of anesthesia ("the postoperative period").

**[0036]** As used herein, "recurrence-specific survival" or "RSS" means the observed length of life from the time of surgical resection to the time of first recurrence of the cancer,

otherwise censored at the time of last follow-up. In RSS, deaths not involving recurrence of cancer are excluded.

**[0037]** As used herein, the term "separate" therapeutic use refers to an administration of at least two active ingredients at the same time or at substantially the same time by different routes.

**[0038]** As used herein, the term "sequential" therapeutic use refers to administration of at least two active ingredients at different times, the administration route being identical or different. More particularly, sequential use refers to the whole administration of one of the active ingredients before administration of the other or others commences. It is thus possible to administer one of the active ingredients over several minutes, hours, or days before administering the other active ingredient or ingredients. There is no simultaneous treatment in this case.

**[0039]** As used herein, the term "simultaneous" therapeutic use refers to the administration of at least two active ingredients by the same route and at the same time or at substantially the same time.

**[0040]** As used herein, the terms "subject", "patient", or "individual" can be an individual organism, a vertebrate, a mammal, or a human. In some embodiments, the subject, patient or individual is a human.

**[0041]** As used herein, the term "therapeutic agent" is intended to mean a compound that, when present in an effective amount, produces a desired therapeutic effect on a subject in need thereof.

**[0042]** "Treating" or "treatment" as used herein covers the treatment of a disease or disorder described herein, in a subject, such as a human, and includes: (i) inhibiting a disease or disorder, *i.e.*, arresting its development; (ii) relieving a disease or disorder, *i.e.*, causing regression of the disorder; (iii) slowing progression of the disorder; and/or (iv) inhibiting, relieving, or slowing progression of one or more symptoms of the disease or disorder. In some embodiments, treatment means that the symptoms associated with the disease are, *e.g.*, alleviated, reduced, cured, or placed in a state of remission.

**[0043]** It is also to be appreciated that the various modes of treatment of disorders as described herein are intended to mean "substantial," which includes total but also less than

total treatment, and wherein some biologically or medically relevant result is achieved. The treatment may be a continuous prolonged treatment for a chronic disease or a single, or few time administrations for the treatment of an acute condition.

**Methods for Improving Survival in Lung Cancer Patients Using Ketamine**

**[0044]** In one aspect, the present disclosure provides a method for prolonging survival of a lung cancer patient undergoing tumor resection surgery comprising administering to the cancer patient an effective amount of ketamine during the tumor resection surgery. The effective amount of ketamine may be administered as a series of bolus doses or as a continuous infusion during the tumor resection surgery. In some embodiments, the ketamine is administered intravenously. The effective amount of ketamine may be administered intraoperatively, preoperatively, and/or postoperatively.

**[0045]** Additionally or alternatively, in some embodiments, the ketamine is infused at a rate of 0.04 mg/kg/hr-2.5 mg/kg/hr. In some embodiments of the methods disclosed herein, the ketamine is infused at a rate of about 0.04 mg/kg/hr, about 0.05 mg/kg/hr, about 0.06 mg/kg/hr, about 0.07 mg/kg/hr, about 0.08 mg/kg/hr, about 0.09 mg/kg/hr, about 0.1 mg/kg/hr, about 0.2 mg/kg/hr, about 0.3 mg/kg/hr, about 0.4 mg/kg/hr, about 0.5 mg/kg/hr, about 0.6 mg/kg/hr, about 0.7 mg/kg/hr, about 0.8 mg/kg/hr, about 0.9 mg/kg/hr, about 1.0 mg/kg/hr, about 1.1 mg/kg/hr, about 1.2 mg/kg/hr, about 1.3 mg/kg/hr, about 1.4 mg/kg/hr, about 1.5 mg/kg/hr, about 1.6 mg/kg/hr, about 1.7 mg/kg/hr, about 1.8 mg/kg/hr, about 1.9 mg/kg/hr, about 2.0 mg/kg/hr, about 2.1 mg/kg/hr, about 2.2 mg/kg/hr, about 2.3 mg/kg/hr, about 2.4 mg/kg/hr, or about 2.5 mg/kg/hr.

**[0046]** Additionally or alternatively, in some embodiments, the ketamine is administered as a bolus of 0.5 mg/kg -4.5 mg/kg. In some embodiments of the methods disclosed herein, the ketamine is administered as a bolus of about 0.04 mg/kg, about 0.05 mg/kg, about 0.06 mg/kg, about 0.07 mg/kg, about 0.08 mg/kg, about 0.09 mg/kg, about 0.1 mg/kg, about 0.2 mg/kg, about 0.3 mg/kg, about 0.4 mg/kg, about 0.5 mg/kg, about 0.6 mg/kg, about 0.7 mg/kg, about 0.8 mg/kg, about 0.9 mg/kg, about 1.0 mg/kg, about 1.1 mg/kg, about 1.2 mg/kg, about 1.3 mg/kg, about 1.4 mg/kg, about 1.5 mg/kg, about 1.6 mg/kg, about 1.7 mg/kg, about 1.8 mg/kg, about 1.9 mg/kg, about 2.0 mg/kg, about 2.1 mg/kg, about 2.2 mg/kg, about 2.3 mg/kg, about 2.4 mg/kg, about 2.5 mg/kg, about 2.6 mg/kg, about 2.7 mg/kg, about 2.8 mg/kg, about 2.9 mg/kg, about 3.0 mg/kg, about 3.1 mg/kg, about 3.2

mg/kg, about 3.3 mg/kg, about 3.4 mg/kg, about 3.5 mg/kg, about 3.6 mg/kg, about 3.7 mg/kg, about 3.8 mg/kg, about 3.9 mg/kg, about 4.0 mg/kg, about 4.1 mg/kg, about 4.2 mg/kg, about 4.3 mg/kg, about 4.4 mg/kg, or about 4.5 mg/kg.

**[0047]** Additionally or alternatively, in some embodiments, the ketamine is administered intramuscularly at a dose of about 4-13 mg/kg. In certain embodiments of the methods disclosed herein, the ketamine is administered intramuscularly at a dose of 4 mg/kg, 5 mg/kg, 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, 10 mg/kg, 11 mg/kg, 12 mg/kg, or 13 mg/kg. Additionally or alternatively, in some embodiments, the ketamine is administered orally at a dose of about 6-10 mg/kg. In certain embodiments of the methods disclosed herein, the ketamine is administered orally at a dose of 6 mg/kg, 7 mg/kg, 8 mg/kg, 9 mg/kg, or 10 mg/kg.

**[0048]** Additionally or alternatively, in some embodiments, the methods of the present technology further comprise administering to the cancer patient an effective amount of an intraoperative opioid analgesic. The intraoperative opioid analgesic may be fentanyl, hydromorphone, morphine, oxycodone, hydrocodone, codeine, meperidine, remifentanil, or sufentanil. The effective amount of the intraoperative opioid analgesic may range from about 1 MME to about 200 MMEs. In certain embodiments, the effective amount of the intraoperative opioid analgesic is about 1 MME to about 20 MMEs, about 20 MMEs to about 45 MMEs, or about 45 MMEs to about 200 MMEs. In some embodiments, the effective amount of the intraoperative opioid analgesic is about 1 MME, about 2 MMEs, about 3 MMEs, about 4 MMEs, about 5 MMEs, about 6 MMEs, about 7 MMEs, about 8 MMEs, about 9 MMEs, about 10 MMEs, about 11 MMEs, about 12 MMEs, about 13 MMEs, about 14 MMEs, about 15 MMEs, about 16 MMEs, about 17 MMEs, about 18 MMEs, about 19 MMEs, about 20 MMEs, about 21 MMEs, about 22 MMEs, about 23 MMEs, about 24 MMEs, about 25 MMEs, about 26 MMEs, about 27 MMEs, about 28 MMEs, about 29 MMEs, about 30 MMEs, about 31 MMEs, about 32 MMEs, about 33 MMEs, about 34 MMEs, about 35 MMEs, about 36 MMEs, about 37 MMEs, about 38 MMEs, about 39 MMEs, about 40-45 MMEs, about 45-50 MMEs, about 50-55 MMEs, about 55-60 MMEs, about 60-65 MMEs, about 65-70 MMEs, about 70-75 MMEs, about 75-80 MMEs, about 80-85 MMEs, about 85-90 MMEs, about 90-95 MMEs, about 95-100 MMEs, about 100-110 MMEs, about 110-120 MMEs, about 120-130 MMEs, about 130-140 MMEs, about 140-150 MMEs, about 150-160 MMEs, about 160-170 MMEs, about

170-180 MMEs, about 180-190 MMEs, or about 190-200 MMEs. Additionally or alternatively, in some embodiments, the effective amount of the intraoperative opioid analgesic is administered as a series of bolus doses or as a continuous infusion during the tumor resection surgery. In certain embodiments, the effective amount of the intraoperative opioid analgesic is administered to the cancer patient prior to incision. Additionally or alternatively, in some embodiments, the effective amount of the intraoperative opioid analgesic is administered intravenously.

**[0049]** Additionally or alternatively, in some embodiments, the method further comprises administering to the cancer patient an effective amount of a local anesthetic solution that comprises one or more of lidocaine, mepivacaine, prilocaine, bupivacaine, etidocaine, ropivacaine, levobupivacaine, cocaine, procaine, tetracaine, chloroprocaine, or benzocaine, and optionally an opioid. In some embodiments, the methods of the present technology further comprise administering to the cancer patient an effective amount of a local anesthetic solution via an epidural catheter before, during and/or after the tumor resection surgery. The effective amount of the local anesthetic solution may range from about 0.05%-4% local anesthetic solution in a volume of 1-10 ml per hour when administered via an epidural catheter. In some embodiments, the effective amount of the local anesthetic solution is about 0.05 %, about 0.06 %, about 0.07 %, about 0.08 %, about 0.09 %, about 0.1 %, about 0.15 %, about 0.2 %, about 0.25 %, about 0.3 %, about 0.35 %, about 0.4 %, about 0.45 %, about 0.5 %, about 0.55 %, about 0.6 %, about 0.65 %, about 0.7 %, about 0.75 %, about 0.8 %, about 0.85 %, about 0.9 %, about 0.95 %, about 1.0 %, about 1.1 %, about 1.2 %, about 1.3 %, about 1.4 %, about 1.5 %, about 1.6 %, about 1.7 %, about 1.8 %, about 1.9 %, about 2.0 %, about 2.1 %, about 2.2 %, about 2.3 %, about 2.4 %, about 2.5 %, about 2.6 %, about 2.7 %, about 2.8 %, about 2.9 %, about 3.0 %, about 3.1 %, about 3.2 %, about 3.3 %, about 3.4 %, about 3.5 %, about 3.6 %, about 3.7 %, about 3.8 %, about 3.9 %, or about 4.0 % local anesthetic solution in a volume of about 1 ml per hour, about 1.5 ml per hour, about 2 ml per hour, about 2.5 ml per hour, about 3 ml per hour, about 3.5 ml per hour, about 4 ml per hour, about 4.5 ml per hour, about 5 ml per hour, about 5.5 ml per hour, about 6 ml per hour, about 6.5 ml per hour, about 7 ml per hour, about 7.5 ml per hour, about 8 ml per hour, about 8.5 ml per hour, about 9 ml per hour, about 9.5 ml per hour, or about 10 ml per hour when administered via an epidural catheter. Additionally or alternatively, in some embodiments, the effective amount of the local anesthetic solution is

administered as a single injection, a series of bolus doses or as a continuous infusion during the tumor resection surgery. Examples of suitable local anesthetics include, but are not limited to, lidocaine, mepivacaine, prilocaine, bupivacaine, etidocaine, ropivacaine, levobupivacaine, cocaine, procaine, tetracaine, chloroprocaine, and benzocaine.

**[0050]** In other embodiments, the effective amount of the local anesthetic solution may be administered before, during and/or after the tumor resection surgery using any regional anesthesia technique directed at nerves innervating the thorax and chest wall (*e.g.*, via serratus plane nerve block, intercostal nerve block, or paravertebral block). The effective amount of the local anesthetic solution may range from about 0.05%-4% local anesthetic solution in a volume of 10-40 ml when administered using any regional anesthesia technique directed at nerves innervating the thorax and chest wall (*e.g.*, via serratus plane nerve block, intercostal nerve block, or paravertebral block). In some embodiments, the effective amount of the local anesthetic solution is about 0.05 %, about 0.06 %, about 0.07 %, about 0.08 %, about 0.09 %, about 0.1 %, about 0.15 %, about 0.2 %, about 0.25 %, about 0.3 %, about 0.35 %, about 0.4 %, about 0.45 %, about 0.5 %, about 0.55 %, about 0.6 %, about 0.65 %, about 0.7 %, about 0.75 %, about 0.8 %, about 0.85 %, about 0.9 %, about 0.95 %, about 1.0 %, about 1.1 %, about 1.2 %, about 1.3 %, about 1.4 %, about 1.5 %, about 1.6 %, about 1.7 %, about 1.8 %, about 1.9 %, about 2.0 %, about 2.1 %, about 2.2 %, about 2.3 %, about 2.4 %, about 2.5 %, about 2.6 %, about 2.7 %, about 2.8 %, about 2.9 %, about 3.0 %, about 3.1 %, about 3.2 %, about 3.3 %, about 3.4 %, about 3.5 %, about 3.6 %, about 3.7 %, about 3.8 %, about 3.9 %, or about 4.0 % local anesthetic solution in a volume of about 10 ml, about 12.5 ml, about 15 ml, about 17.5 ml, about 20 ml, about 22.5 ml, about 25 ml, about 27.5 ml, about 30 ml, about 32.5 ml, about 35 ml, about 37.5 ml, or about 40 ml when administered using any regional anesthesia technique directed at nerves innervating the thorax and chest wall (*e.g.*, via serratus plane nerve block, intercostal nerve block, or paravertebral block). Examples of suitable local anesthetics include, but are not limited to, lidocaine, mepivacaine, prilocaine, bupivacaine, etidocaine, ropivacaine, levobupivacaine, cocaine, procaine, tetracaine, chloroprocaine, and benzocaine.

**[0051]** Additionally or alternatively, in certain embodiments, the local anesthetic solution may further comprise an opioid (*e.g.*, fentanyl, hydromorphone, morphine, oxycodone, hydrocodone, codeine, meperidine, remifentanil, or sufentanil). In some embodiments, the local anesthetic solution may comprise 0.5 mcg/ml-50 mcg/ml opioid. In certain

embodiments, the local anesthetic solution may comprise about 0.5 mcg/ml, about 0.6 mcg/ml, about 0.7 mcg/ml, about 0.8 mcg/ml, about 0.9 mcg/ml, about 1.0 mcg/ml, about 1.5 mcg/ml, about 2.0 mcg/ml, about 2.5 mcg/ml, about 3.0 mcg/ml, about 3.5 mcg/ml, about 4.0 mcg/ml, about 4.5 mcg/ml, about 5.0 mcg/ml, about 5.5 mcg/ml, about 6.0 mcg/ml, about 6.5 mcg/ml, about 7.0 mcg/ml, about 7.5 mcg/ml, about 8.0 mcg/ml, about 8.5 mcg/ml, about 9.0 mcg/ml, about 10 mcg/ml, about 15 mcg/ml, about 20 mcg/ml, about 25 mcg/ml, about 30 mcg/ml, about 35 mcg/ml, about 40 mcg/ml, about 45 mcg/ml, or about 50 mcg/ml.

**[0052]** Additionally or alternatively, in some embodiments, the methods of the present technology further comprise administering to the cancer patient an effective amount of a post-operative opioid analgesic after the tumor resection surgery. Examples of post-operative opioid analgesics include, but are not limited to, fentanyl, hydromorphone, morphine, oxycodone, hydrocodone, codeine, meperidine, remifentanil, or sufentanil. In some embodiments, the post-operative opioid analgesic and the intraoperative opioid analgesic are the same opioid analgesic or different opioid analgesics. In other embodiments, the effective amount of the post-operative opioid analgesic and the effective amount of the intraoperative opioid analgesic are the same or different. In some embodiments, the effective amount of the post-operative opioid analgesic is administered to the cancer patient as a bolus of about 0.005 mg to about 100 mg. Additionally or alternatively, in some embodiments, the effective amount of the post-operative opioid analgesic is administered to the cancer patient as a bolus of about 0.005 mg, about 0.006 mg, about 0.007 mg, about 0.008 mg, about 0.009 mg, about 0.01 mg, about 0.02 mg, about 0.03 mg, about 0.04 mg, about 0.05 mg, about 0.06 mg, about 0.07 mg, about 0.08 mg, about 0.09 mg, about 0.1 mg, about 0.2 mg, about 0.3 mg, about 0.4 mg, about 0.5 mg, about 0.6 mg, about 0.7 mg, about 0.8 mg, about 0.9 mg, about 1-5 mg, about 5-10 mg, about 1-5 mg, about 5-10 mg, about 1-5 mg, about 5-10 mg, about 1-5 mg, about 5-10 mg, about 10-15 mg, about 15-20 mg, about 20-25 mg, about 25-30 mg, about 30-35 mg, about 35-40 mg, about 40-45 mg, about 45-50 mg, about 50-55 mg, about 55-60 mg, about 60-65 mg, about 65-70 mg, about 70-75 mg, about 75-80 mg, about 80-85 mg, about 85-90 mg, about 90-95 mg, or about 95-100 mg. In other embodiments, the effective amount of the post-operative opioid analgesic may be continuously delivered to the cancer patient at a per hour rate of about 0.01 mg/hr to about 10 mg/hr. In certain embodiments, the effective

amount of the post-operative opioid analgesic is continuously delivered to the cancer patient at a per hour rate of about 0.01 mg/hr, about 0.02 mg/hr, about 0.03 mg/hr, about 0.04 mg/hr, about 0.05 mg/hr, about 0.06 mg/hr, about 0.07 mg/hr, about 0.08 mg/hr, about 0.09 mg/hr, about 0.1 mg/hr, about 0.2 mg/hr, about 0.3 mg/hr, about 0.4 mg/hr, about 0.5 mg/hr, about 0.6 mg/hr, about 0.7 mg/hr, about 0.8 mg/hr, about 0.9 mg/hr, about 1 mg/hr, about 1.5 mg/hr, about 2 mg/hr, about 2.5 mg/hr, about 3 mg/hr, about 3.5 mg/hr, about 4 mg/hr, about 4.5 mg/hr, about 5 mg/hr, about 5.5 mg/hr, about 6 mg/hr, about 6.5 mg/hr, about 7 mg/hr, about 7.5 mg/hr, about 8 mg/hr, about 8.5 mg/hr, about 9 mg/hr, about 9.5 mg/hr, or about 10 mg/hr. Additionally or alternatively, in some embodiments, the effective amount of the post-operative opioid analgesic is administered intravenously, orally, or transdermally.

**[0053]** In other embodiments, the methods of the present technology further comprise administering to the cancer patient an effective amount of an opioid-free post-operative analgesic after the tumor resection surgery. Examples of suitable opioid-free post-operative analgesics include, but are not limited to, lidocaine, mepivacaine, prilocaine, bupivacaine, etidocaine, ropivacaine, levobupivacaine, cocaine, procaine, tetracaine, chloroprocaine, and benzocaine. In some embodiments, the opioid-free post-operative analgesic and the opioid-free intraoperative analgesic are the same analgesic or different analgesics. In other embodiments, the effective amount of the opioid-free post-operative analgesic and the effective amount of the opioid-free intraoperative analgesic are the same or different.

**[0054]** In any and all embodiments of the methods disclosed herein, the cancer patient exhibits stage I, stage II or stage III lung cancer. Additionally or alternatively, in some embodiments, the cancer patient has been diagnosed with lung adenocarcinoma (LUAD). The histologic subtype of the lung adenocarcinoma may be lepidic, acinar, papillary, micropapillary, solid or unknown.

**[0055]** In any of the preceding embodiments of the methods disclosed herein, the cancer patient has received an adjuvant therapy. The adjuvant therapy may be chemotherapy, lobectomy, radiation therapy or chemoradiation therapy. Additionally or alternatively, in some embodiments of the methods disclosed herein, the patient is human.

## EXAMPLES

**[0056]** The present technology is further illustrated by the following Examples, which should not be construed as limiting in any way.

***Example 1: Methods***

*Patients*

**[0057]** After institutional review board approval, a prospectively maintained database of 740 patients with primary pathological stage I-III LUAD who underwent a complete (R0) resection from 2010 to 2019 was retrospectively reviewed. Demographic, radiographic, pathologic, genomic and follow-up patient data were reviewed. Predominant invasive LUAD histologic subtype was designated as either lepidic, acinar, papillary, micropapillary, solid or unknown. The Elixhauser-van Walraven (EvW) score, a well-validated co-morbidity index, was used to quantify patient comorbid status.

**[0058]** All patients consented to next generation sequencing (NGS; MSK-IMPACT) on their primary tumor. The CONSORT diagram shows exclusion criteria for the patient cohort (**FIG. 2**). Metachronous and synchronous tumors were excluded with metachronous tumors differentiated from recurrent tumors in accordance with the Martini and Melamed criteria, as previously described in Martini N, Melamed MR. *J Thorac Cardiovasc Surg.* 70(4):606-612 (1975).

*MSK-IMPACT Sequencing*

**[0059]** Tumor genomic profiling was performed on all 740 LUAD samples using the MSK-IMPACT platform (described in Cheng DT, *et al.*, *J Mol Diagn.* 17: 251-264 (2015)). Genomic factors of interest were selected for further analysis, including tumor mutational burden (TMB), fraction genome altered (FGA), and all genes altered at $\geq$5% frequency in the cohort. Also included were the ten canonical oncologic signaling pathways (cell cycle, Hippo, Myc, Notch, Nrf2, Pi3K, RTK/RAS, TGFβ, p53, and Wnt).

**[0060]** Sequencing breadth of the MSK-IMPACT panel has increased over time resulting in 16, 201, and 583 patients from this cohort sequenced with 341-, 410-, and 468-gene panels, respectively (Cheng DT, *et al.*, *J Mol Diagn.* 17: 251-264 (2015)). Tumor mutation burden (TMB) was defined as the total number of nonsynonymous coding variants per megabase (Mb) and was normalized by each panel size (0.98, 1.06, 1.22 Mb in the 341-, 410-, 468-

gene panels, respectively). The total number of mutations by length of coding region was divided by the total number of panels. Fraction genome altered (FGA) was defined as the number of bases in sequenced genomic segments with log2 copy number fold change >0.2 or <-0.2 over the total number of bases in all sequenced segments. Known mutations and copy number alterations which have been described to activate oncogenes or inactivate tumor suppressor genes were identified using the proprietary OncoKB Knowledge Base. This system was necessary to distinguish between those mutations and alterations with known or presumed functional implications against benign variants or those with unknown clinical significance (Chakravarty D *et al., JCO Precision Oncology*. 1:1-84 6 (2017)).

**[0061]** A total of 121 genes were identified *a priori* in the 10 oncogenic signaling pathways. Zhou J *et al., Clinical Cancer Research.* 25(24):7475-7484 (2019). A pathway was considered altered in a tumor if at least one gene within the corresponding pathway template was altered. For analysis of co-occurrence and mutual exclusivity, all genes known to be drivers in LUAD were assessed (Chakravarty D *et al., JCO Precision Oncology*. 1:1-84 6 (2017)). Mutual exclusivity and co-occurrence alterations in genes and oncogenic signaling pathways was assessed using Fisher's exact test and P values were adjusted to correct for multiple comparisons using the false discovery rate (FDR) correction.

*Intraoperative Analgesic Agents*

**[0062]** Doses of fentanyl, hydromorphone, and morphine administered intraoperatively were extracted from electronic anesthesia records, converted to oral morphine milligram equivalents (MMEs), and summed to give total intraoperative dose, where 10 MMEs is equal to 50 mcg fentanyl IV (a standard intraoperative bolus dose) (**FIG. 6A**). Intraoperative analgesic agents included hydromorphone, fentanyl, and morphine, with the majority of patients receiving fentanyl (**FIG. 6A**). Total intraoperative morphine milligram equivalents (MMEs) were evaluated in a continuous dose-dependent manner. Intraoperative administration of ketamine or dexmedetomidine was also identified and quantified. Patients who received both dexmedetomidine and ketamine (N=8) were included in either the ketamine or the dexmedetomidine group depending on highest infusion dose (calculated as a weighted average based on duration and rate of infusion).

*Immunohistochemistry on LUAD Samples*

**[0063]** Immunohistochemical staining was performed on ten patient samples using a hydrogen peroxidase method. Frozen tissue samples were chosen based on tissue availability from a subset of available tissue in this patient cohort.

**[0064]** The LUAD samples were run in duplicate against matched adjacent non-tumor lung tissue samples to detect expression levels of the MOR. Tissue samples were homogenized in PBS (10mg in 100µl PBS) and samples were centrifuged at 3000rpm for 15 minutes at which point, the supernatant was removed and run on quantitative sandwich enzyme linked immunosorbent assay (ELISA) kits for the mu opioid receptor (MOR) purchased from MyBioSource, Inc. (San Diego, CA). A preliminary bicinchoninic acid protein assay was performed to quantify total protein in each sample and normalize all samples prior to MOR ELISA analysis. ELISA sensitivities were <7.81pg/ml with intra-assay coefficient of variability (CV) <8% and inter-assay CV <10% precision. Median optical density (OD) levels for all tumor samples were obtained and compared against non-tumor matched controls. Standard OD levels were analyzed on a logistic regression and median sample concentrations were estimated for both the tumor and non-tumor specimens. Standard error of the mean was estimated for tumor and non-tumor MOR sample composite concentrations.

*Statistical Analysis*

**[0065]** The primary objective of the study was to quantify the association between intraoperative opioid dose and oncologic outcomes. The primary outcome was recurrence-specific survival (RSS). Time to event was determined from the time of surgical resection to the time of first recurrence, otherwise censored at the time of last follow-up. RSS was chosen in place of the alternative recurrence-free survival (RFS), time to recurrence or death from any cause, in order to determine whether opioids and the adjuncts were associated with disease progression in stage I-III LUAD. The secondary outcome was cancer specific survival (OS), which was defined as time to death from any cause.

**[0066]** To estimate the association between intraoperative opioids and oncologic outcomes, univariable and multivariable Cox proportional hazard regressions were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs), treating intraoperative MME as a continuous variable and adjunct administration as a categorical variable. For each endpoint (RFS and OS), variables with a p-value of $< 0.1$ were included in the multivariable model,

while retaining some clinically relevant variables. In the case of RSS analysis, patients who died without recurrence were considered censored using a cause-specific hazard model rather than a sub-distribution hazard model; in this etiological framework, the cause-specific hazard is more appropriate as it directly quantifies the hazard among subjects that are actually at risk of developing the event of interest, whereas in the sub-distribution hazard model individuals that experienced the competing event remain in the risk set. Each model was designed for the OS and RSS outcomes and were adjusted for relevant clinicopathological features. An additional multivariable model was constructed for each genomic factor of interest, for each outcome, by adding to the multivariable model a term for presence of factor alteration and a term for interaction between the factor and opioid dose.

**[0067]** To better visualize the impact of incremental increases in intraoperative MMEs on outcomes, predicted 5-year OS and RSS estimates, corresponding to a range of MMEs, were generated based on the final Multivariable Cox regression analyses (MVAs) for a representative patient. KM survival curves were used for the categorical adjunct variables.

**[0068]** Survival endpoints were measured from the time of surgery and patients were censored at the time of last follow-up. OS and CSS were estimated using the Kaplan-Meier (KM) approach by MME and compared using log-rank tests. Median follow-up duration was estimated using the Kaplan-Meier (KM) method.

**[0069]** All univariable models were stratified by pathologic stage. Multivariable Cox regression analyses (MVA) against each outcome were constructed in a backward elimination procedure. The set of factors for each MVA were confirmed by LASSO variable selection procedure. Because of their clinical relevance to oncologic outcomes, pathologic stage and procedure type were included in the MVAs regardless of statistical significance. Intraoperative MMEs, the two adjunct variables, and procedure type were included in the MVA for both survival outcomes. The proportional hazards assumptions were assessed using scaled Schoenfeld residuals. The linearity assumption of continuous variables was assessed using restricted cubic splines in the models for both outcomes. All statistical tests were two-sided with $p<0.05$ indicating statistical significance. R 3.6.2 (R Core Team, Vienna, Austria) was used for statistical analyses.

*Predicted MME Curves*

**[0070]** The predicted 5-year overall survival (OS) and recurrence-specific survival (RSS) estimate curves were generated based on the most frequently observed characteristics or median value for each continuous variable in the MVA (papillary/acinar histologic subtype, median Exlihauser-van Walraven score, lobectomy procedure, median age, and pathologic stage I). These predicted OS and RSS estimates by MME curve were generated for the MVAs without genomic factors.

***Example 2: Patient Demographics***

**[0071]** Seven hundred forty patients were included in the study. The majority were female (N=489, 66%) and most were former or current smokers (N=543, 73%). The median age at surgery was 68 years (interquartile range [IQR], 61-73 years) and median Elixhauser-van Walraven (EvW) comorbidity score was 12 (IQR, 7-15; **FIG. 3** and **FIG. 4**).

***Example 3: Clinicopathologic and Analgesic Variables***

**[0072]** Median intraoperative MMEs received by the overall cohort was 42 (IQR, 30-60 MMEs). Patients who received dexmedetomidine received significantly less intraoperative MMEs (median 40, 30-57) compared to the no adjunct cohort (median 50, IQR 30-61; **FIG. 4**). All patients had pathologically diagnosed LUAD which were differentiated into groups based on histologic subtype: lepidic (N=136, 18%), acinar/papillary (N=441, 60%), micropapillary/solid (N=153, 21%), and unknown (N=10, 1.4%). Four hundred fifty-six patients were pathologic stage I (62%), 157 patients (21%) were stage II and 127 patients (17%) were stage III (**FIG. 3**). Thirteen percent of the cohort (N=96) received induction chemotherapy and most patients received a lobectomy (N=610, 82%). Almost a third (N=227, 31%) received adjuvant therapy, 31 patients (4.2%) received combination chemoradiation, 153 patients (21%) received chemotherapy alone, and 29 patients (3.9%) received radiation therapy (**FIG. 4**). Median follow-up duration was 2.74 years (IQR, 1.76 – 3.82).

***Example 4: Association between Intraoperative Analgesics and Outcomes***

**[0073]** Five-year RSS was 61.8% (95% CI, 54.7 – 69.7%) and OS was 74.4% (95% CI,68.6 – 80.6%). There were 95 deaths and 160 locoregional or distant recurrence events in this observation window. The linearity assumptions for intraoperative MME were not violated for both RSS (p=0.32) and OS (p=0.35), hence this primary exposure factor was treated as a continuous variable in the analyses. Intraoperative opioid dose was not significantly

associated with RSS (**FIG. 3**) on either univariable or multivariable analysis. The adjunct, ketamine, was significantly associated with improved RSS compared to patients who received no adjunct therapy on both univariable (HR 0.51, 95% CI 0.28 – 0.91; p=0.023) and multivariable analysis (HR 0.44, 95% CI 0.24 – 0.80; p=0.007; **FIG. 5**, **FIG. 3**, **FIG. 1A**). As shown in the MVA, when all else is kept equal (two patients: with same age, VWscore, Procedure, histology and pathologic stage, and the same MME [could be both 0, could be both 100 units]), the patient with Ketamine has 66% lower hazard of recurrence compared to the patient with no adjunct (HR=0.55, 95% CI 0.24 – 0.80, p=0.007).

**[0074]** Higher intraoperative MME was associated with worse OS on both univariable (HR 1.09 per 10 MME, 95% CI 1.02 – 1.16; p=0.011) and multivariable analysis (HR 1.09 per 10 MME, 95% CI 1.02-1.17; p=0.010). Notably, there were no significant differences in OS with ketamine administration. Dexmedetomidine administration was not significantly associated with either outcome (**FIG. 3**, **FIG. 1B**, **FIG. 5**).

**[0075]** Taken together, these results demonstrate that the use of ketamine as an anesthetic adjunct is protective against recurrence of lung cancer. The divide between a worse OS-opioid dose result and improved RSS-ketamine result supports the theory of different underlying mechanisms for these drugs.

**[0076]** These results demonstrate that combination therapy with intraoperative opioid analgesics and ketamine are useful in prolonging survival of a lung cancer patient undergoing tumor resection surgery.

## EQUIVALENTS

**[0077]** The present technology is not to be limited in terms of the particular embodiments described in this application, which are intended as single illustrations of individual aspects of the present technology. Many modifications and variations of this present technology can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. Functionally equivalent methods and apparatuses within the scope of the present technology, in addition to those enumerated herein, will be apparent to those skilled in the art from the foregoing descriptions. Such modifications and variations are intended to fall within the scope of the present technology. It is to be understood that this present technology is not limited to particular methods, reagents, compounds compositions or biological systems, which can, of course, vary. It is also to be understood that the

terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting.

**[0078]** In addition, where features or aspects of the disclosure are described in terms of Markush groups, those skilled in the art will recognize that the disclosure is also thereby described in terms of any individual member or subgroup of members of the Markush group.

**[0079]** As will be understood by one skilled in the art, for any and all purposes, particularly in terms of providing a written description, all ranges disclosed herein also encompass any and all possible subranges and combinations of subranges thereof. Any listed range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, *etc.* As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, *etc.* As will also be understood by one skilled in the art all language such as "up to," "at least," "greater than," "less than," and the like, include the number recited and refer to ranges which can be subsequently broken down into subranges as discussed above. Finally, as will be understood by one skilled in the art, a range includes each individual member. Thus, for example, a group having 1-3 cells refers to groups having 1, 2, or 3 cells. Similarly, a group having 1-5 cells refers to groups having 1, 2, 3, 4, or 5 cells, and so forth.

**[0080]** All patents, patent applications, provisional applications, and publications referred to or cited herein are incorporated by reference in their entirety, including all FIGs. and tables, to the extent they are not inconsistent with the explicit teachings of this specification.

## Claims

1. A method for prolonging survival of a lung cancer patient undergoing tumor resection surgery comprising administering to the cancer patient an effective amount of ketamine during the tumor resection surgery.

2. The method of claim 1, wherein the ketamine is administered intravenously.

3. The method of claim 1 or 2, wherein the effective amount of ketamine is administered as a series of bolus doses or as a continuous infusion during the tumor resection surgery.

4. The method of claim 3, wherein the ketamine is infused at a rate of 0.04 mg/kg/hr-2.5 mg/kg/hr.

5. The method of claim 3, wherein the ketamine is administered as a bolus of 0.5 mg/kg -4.5 mg/kg.

6. The method of any one of claims 1-5, wherein the effective amount of ketamine is administered intraoperatively, preoperatively, and/or postoperatively.

7. The method of any one of claims 1-6, wherein the ketamine is administered intramuscularly at a dose of 4-13 mg/kg.

8. The method of any one of claims 1-7, wherein the ketamine is administered orally at a dose of 6-10 mg/kg.

9. The method of any one of claims 1-8, comprising administering to the cancer patient an effective amount of an intraoperative opioid analgesic.

10. The method of claim 9, wherein the intraoperative opioid analgesic is fentanyl, hydromorphone, morphine, oxycodone, hydrocodone, codeine, meperidine, remifentanil, or sufentanil.

11. The method of claim 9 or 10, wherein the effective amount of the intraoperative opioid analgesic is about 1 MME to about 20 MMEs.

12. The method of claim 9 or 10, wherein the effective amount of the intraoperative opioid analgesic is about 20 MMEs to about 45 MMEs.

13. The method of claim 9 or 10, wherein the effective amount of the intraoperative opioid analgesic is about 45 MMEs to about 200 MMEs.

14. The method of any one of claims 9-13, wherein the intraoperative opioid analgesic is administered intravenously.

15. The method of any one of claims 9-14, wherein the effective amount of the intraoperative opioid analgesic is administered as a series of bolus doses or as a continuous infusion during the tumor resection surgery.

16. The method of any one of claims 9-15, wherein the effective amount of the intraoperative opioid analgesic is administered to the cancer patient prior to incision.

17. The method of any one of claims 1-16, further comprising administering to the cancer patient an effective amount of a local anesthetic solution that comprises one or more of lidocaine, mepivacaine, prilocaine, bupivacaine, etidocaine, ropivacaine, levobupivacaine, cocaine, procaine, tetracaine, chloroprocaine, or benzocaine, and optionally an opioid.

18. The method of claim 17, wherein the local anesthetic solution is administered via an epidural catheter, via a serratus plane nerve block or via an intercostal nerve block during and/or after the tumor resection surgery.

19. The method of any one of claims 1-18, further comprising administering to the cancer patient an effective amount of a post-operative opioid analgesic after the tumor resection surgery.

20 The method of claim 19, wherein the post-operative opioid analgesic is fentanyl, hydromorphone, morphine, oxycodone, hydrocodone, codeine, meperidine, remifentanil, or sufentanil.

21. The method of claim 19 or 20, wherein the post-operative opioid analgesic and the intraoperative opioid analgesic are the same or different.

22. The method of any one of claims 19-21, wherein the effective amount of the post-operative opioid analgesic and the effective amount of the intraoperative opioid analgesic are the same or different.

23. The method of any one of claims 1-22, wherein the cancer patient exhibits stage I, stage II or stage III lung cancer.

24. The method of any one of claims 1-23, wherein the cancer patient has been diagnosed with lung adenocarcinoma (LUAD).

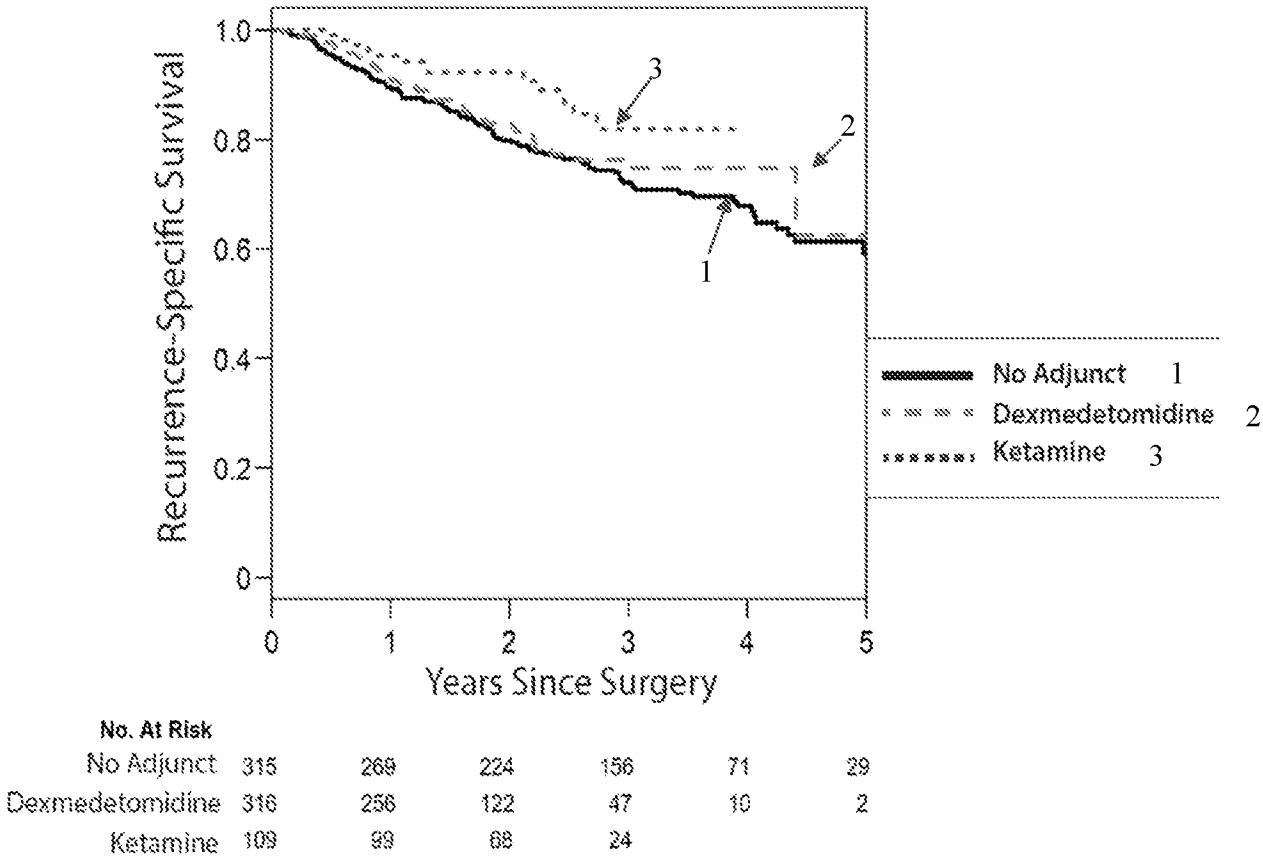
25. The method of claim 24, wherein the lung adenocarcinoma has a histologic subtype selected from among lepidic, acinar, papillary, micropapillary, solid or unknown.

26. The method of any one of claims 1-25, wherein the cancer patient has received an adjuvant therapy.

27. The method of claim 26, wherein the adjuvant therapy is chemotherapy, lobectomy, radiation therapy or chemoradiation therapy.

28. The method of any one of claims 1-27, wherein the cancer patient is human.

# FIG. 1A




| No. At Risk | | | | | | |
|---|---|---|---|---|---|---|
| No Adjunct | 315 | 269 | 224 | 156 | 71 | 29 |
| Dexmedetomidine | 316 | 256 | 122 | 47 | 10 | 2 |
| Ketamine | 109 | 99 | 68 | 24 | | |

**FIG. 1B**

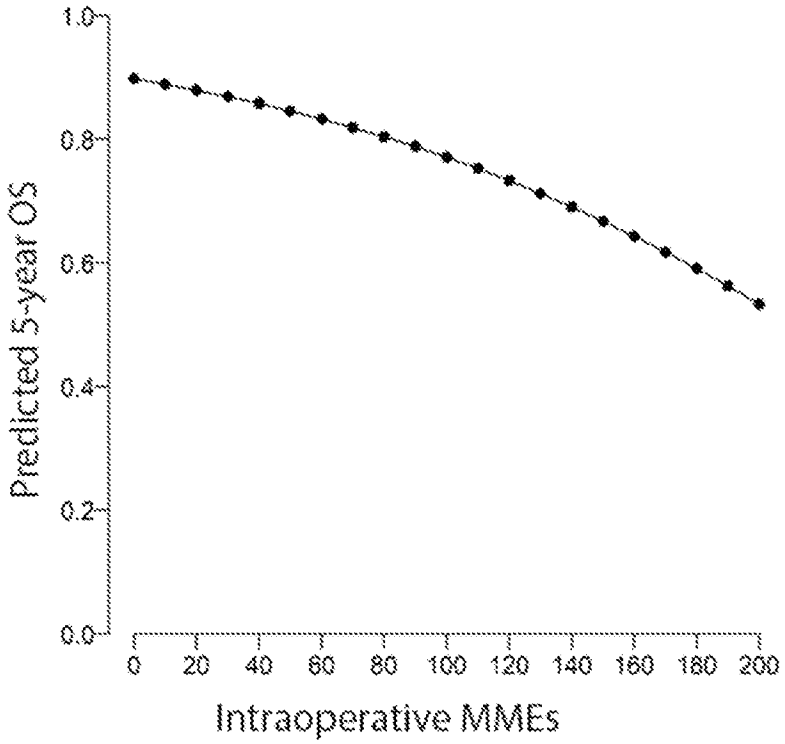

Predicted 5-year OS
1.0
0.8
0.6
0.4
0.2
0.0
0 20 40 60 80 100 120 140 160 180 200
Intraoperative MMEs

**FIG. 1C**

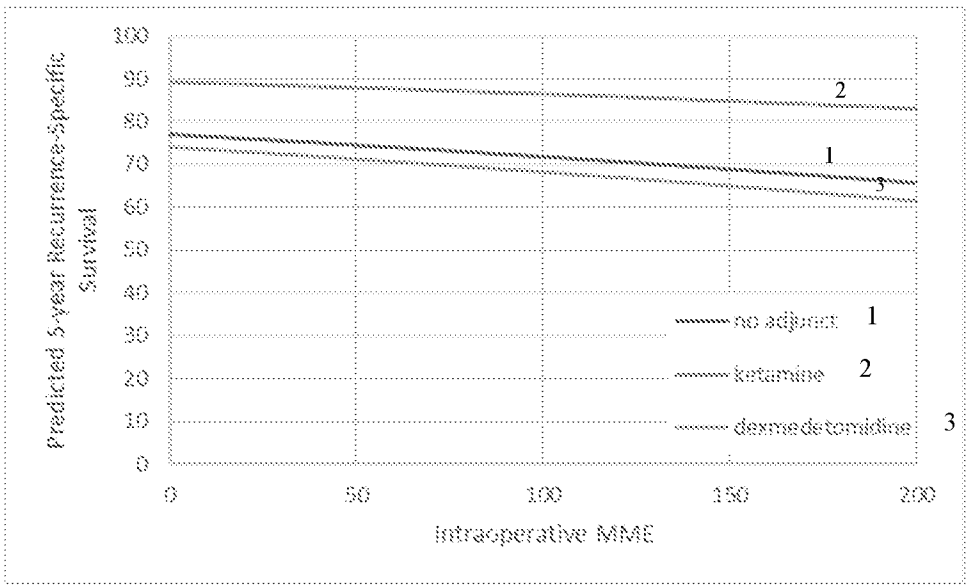
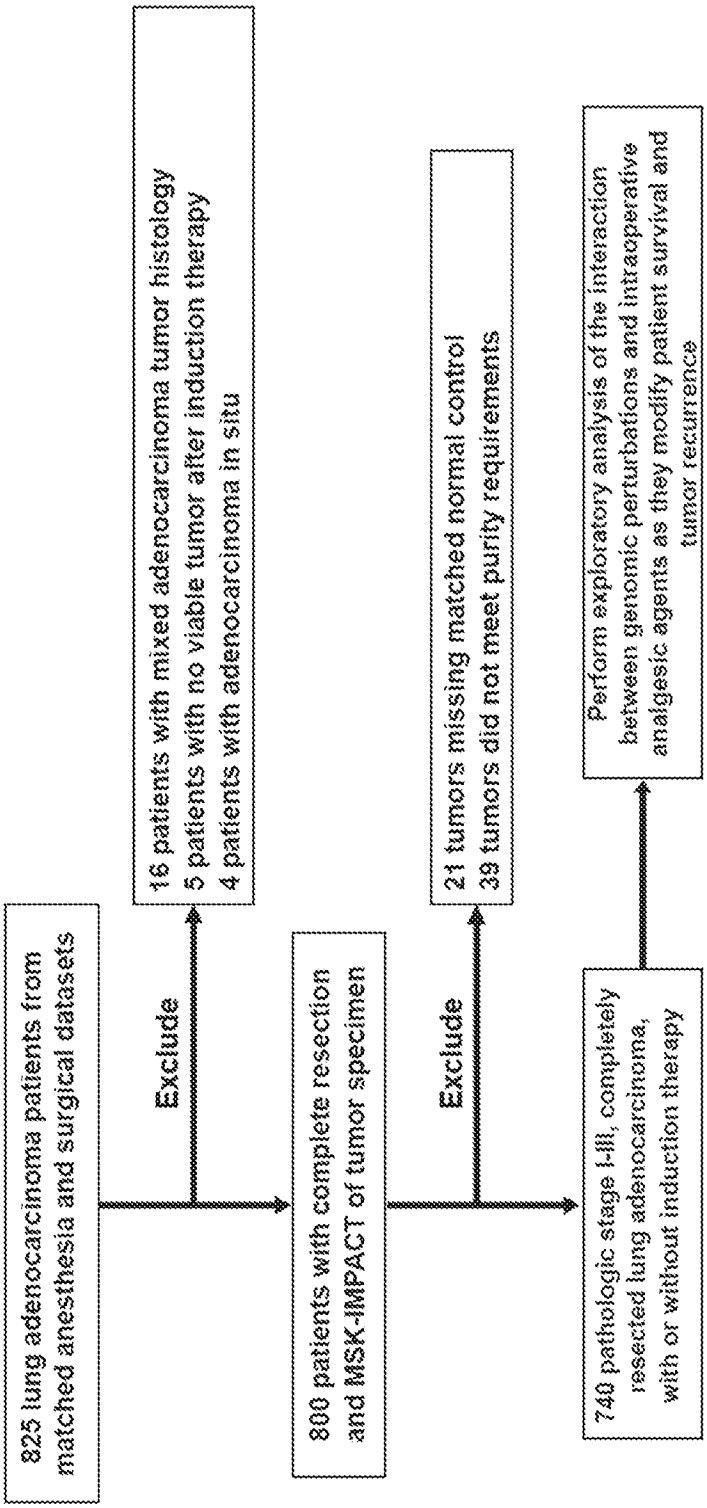
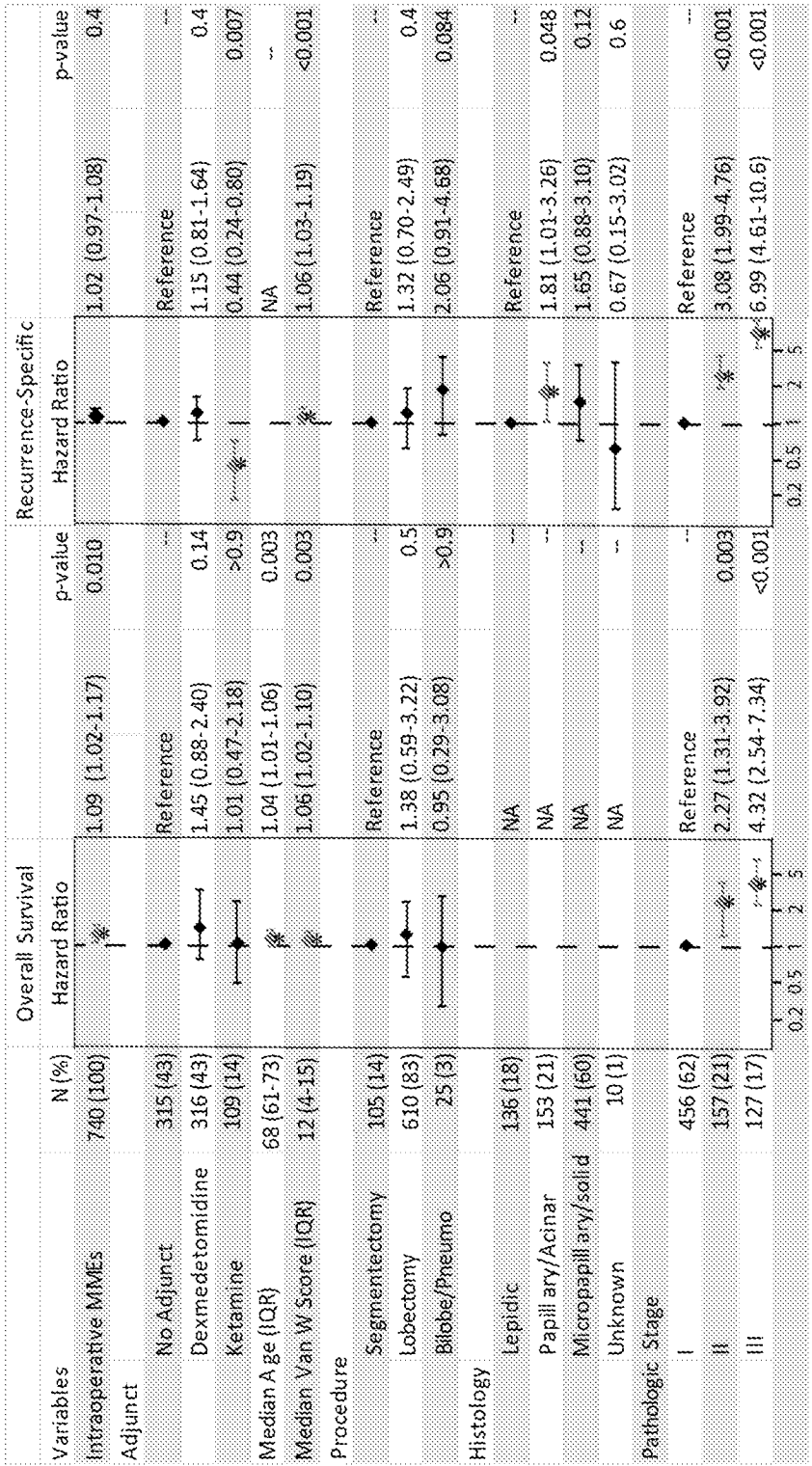

Predicted 5-year Recurrence-Specific Survival
100
90
80
70
60
50
40
30
20
10
0
0 50 100 150 200
Intraoperative MME
2
1
3
no adjuvant 1
ketamine 2
dexmedetomidine 3

**FIG. 2**


825 lung adenocarcinoma patients from matched anesthesia and surgical datasets
Exclude
16 patients with mixed adenocarcinoma tumor histology
5 patients with no viable tumor after induction therapy
4 patients with adenocarcinoma in situ
800 patients with complete resection and MSK-IMPACT of tumor specimen
Exclude
21 tumors missing matched normal control
39 tumors did not meet purity requirements
740 pathologic stage I-III, completely resected lung adenocarcinoma, with or without induction therapy
Perform exploratory analysis of the interaction between genomic perturbations and intraoperative analgesic agents as they modify patient survival and tumor recurrence

# FIG. 3


Overall Survival
Recurrence-Specific
Variables
N (%)
Hazard Ratio
p-value
Hazard Ratio
p-value
Intraoperative MMEs
740 (100)
1.09 (1.02-1.17)
0.010
1.02 (0.97-1.08)
0.4
Adjunct
No Adjunct
315 (43)
Reference
--
Reference
--
Dexmedetomidine
316 (43)
1.45 (0.88-2.40)
0.14
1.15 (0.81-1.64)
0.4
Ketamine
109 (14)
1.01 (0.47-2.18)
>0.9
0.44 (0.24-0.80)
0.007
Median Age (IQR)
68 (61-73)
1.04 (1.01-1.06)
0.003
NA
--
Median Van W Score (IQR)
12 (4-15)
1.06 (1.02-1.10)
0.003
1.06 (1.03-1.19)
<0.001
Procedure
Segmentectomy
105 (14)
Reference
--
Reference
--
Lobectomy
610 (83)
1.38 (0.59-3.22)
0.5
1.32 (0.70-2.49)
0.4
Bilobe/Pneumo
25 (3)
0.95 (0.29-3.08)
>0.9
2.06 (0.91-4.68)
0.084
Histology
Lepidic
136 (18)
NA
--
Reference
--
Papillary/Acinar
153 (21)
NA
--
1.81 (1.01-3.26)
0.048
Micropapillary/solid
441 (60)
NA
--
1.65 (0.88-3.10)
0.12
Unknown
10 (1)
NA
--
0.67 (0.15-3.02)
0.6
Pathologic Stage
I
456 (62)
Reference
--
Reference
--
II
157 (21)
2.27 (1.31-3.92)
0.003
3.08 (1.99-4.76)
<0.001
III
127 (17)
4.32 (2.54-7.34)
<0.001
6.99 (4.61-10.6)
<0.001
0.2 0.5 1 2 5
0.2 0.5 1 2 5

Red: *

# FIG. 4

| Characteristic | Overall (N = 740) | No Adjunct (N = 315) | Dexmedetomidine (N = 316) | Ketamine (N = 109) | p-value |
|---|---|---|---|---|---|
| Intraoperative MME | 42 (30, 60) | 50 (30, 61) | 40 (30, 57) | 48 (40, 67) | 0.01 |
| Epidural | 264 (36%) | 182 (58%) | 54 (17%) | 28 (26%) | <0.001 |
| Female | 489 (66%) | 217 (69%) | 195 (62%) | 77 (71%) | 0.09 |
| BMI | 26.6 (23.6, 30.1) | 26.2 (23.2, 29.9) | 26.7 (23.6, 30.1) | 27.0 (24.0, 30.6) | 0.4 |
| Smoking Status | | | | | 0.018 |
| Current | 53 (7.2%) | 28 (8.9%) | 22 (7.0%) | 3 (2.8%) | |
| Former | 490 (66%) | 218 (69%) | 194 (61%) | 78 (72%) | |
| Never | 197 (27%) | 69 (22%) | 100 (32%) | 28 (26%) | |
| E-W Score | 12.0 (4.0, 15.0) | 12.0 (7.0, 14.0) | 12.0 (4.0, 15.0) | 12.0 (4.0, 13.0) | 0.7 |
| Induction therapy | 96 (13%) | 51 (16%) | 26 (8.2%) | 19 (17%) | 0.004 |
| Adjuvant therapy | | | | | 0.044 |
| None | 513 (69%) | 204 (65%) | 234 (74%) | 75 (69%) | |
| Chemotherapy | 153 (21%) | 66 (21%) | 62 (20%) | 25 (23%) | |
| Radiation Therapy | 29 (3.9%) | 20 (6.3%) | 7 (2.2%) | 2 (1.8%) | |
| Chemoradiation | 31 (4.2%) | 16 (5.1%) | 9 (2.8%) | 6 (5.5%) | |
| Unknown | 14 (1.9%) | 9 (2.9%) | 4 (1.3%) | 1 (0.9%) | |
| Surgery length (min) | 196 (162, 238) | 188 (156, 229) | 196 (165, 241) | 212 (175, 262) | <0.001 |
| EBL > 500 | 24 (3.2%) | 8 (2.5%) | 11 (3.5%) | 5 (4.6%) | 0.5 |
| Intraop time MAP below 65 bmp (mins) | 14 (5, 29) | 17 (6, 33) | 14 (6, 26) | 8 (1, 22) | <0.001 |
| Intraop time HR above 100 bmp (mins) | 1 (0, 4) | 1 (0, 4) | 1 (0, 4) | 1 (0, 6) | 0.1 |
| Intraop time temp below 35.5°C (mins) | 10 (0, 74) | 11 (0, 73) | 9 (0, 77) | 8 (0, 73) | 0.8 |

Data are median (interquartile range) or no. (%). MME, morphine milligram equivalents; BMI, body mass index; EBL, estimate blood loss; MAP, mean arterial pressure; HR, heart rate

# FIG. 5

| | | Overall Survival | | | Recurrence-Specific Survival | | |
|---|---|---|---|---|---|---|---|
| Covariate | N (%) | HR | 95% CI | p-value | HR | 95% CI | p-value |
| **Intraoperative MMEs** | 740 (100) | 1.09 | 1.02, 1.16 | 0.011 | 1.02 | 0.97, 1.08 | 0.4 |
| **Anesthetic Adjuncts** | | | | 0.12 | | | 0.023 |
| **No Adjunct** | 315 (43) | — | — | | — | — | |
| **Dexmedetomidine** | 316 (43) | 1.64 | 1.00, 2.70 | | 1.20 | 0.85, 1.70 | |
| **Ketamine** | 109 (14) | 0.98 | 0.46, 2.10 | | 0.51 | 0.28, 0.91 | |
| **Age at time of surgery** | | 1.04 | 1.01, 1.06 | 0.003 | 0.99 | 0.97, 1.00 | 0.095 |
| **Sex** | | | | 0.2 | | | 0.3 |
| **Female** | 489 (66) | — | — | | — | — | |
| **Male** | 251 (34) | 1.35 | 0.89, 2.05 | | 1.20 | 0.87, 1.65 | |
| **Smoking status** | | | | 0.3 | | | 0.3 |
| **Never** | 197 (27) | — | — | | — | — | |
| **Former** | 490 (66) | 1.51 | 0.91, 2.51 | | 0.75 | 0.53, 1.05 | |
| **Current** | 53 (7.2) | 1.65 | 0.72, 3.80 | | 0.84 | 0.43, 1.61 | |
| **EvW Score** | 740 (100) | 1.06 | 1.02, 1.10 | 0.002 | 1.06 | 1.03, 1.09 | <0.001 |
| **Induction** | | | | 0.3 | | | 0.7 |
| **No** | 644 (87) | — | — | | — | — | |
| **Yes** | 96 (13) | 1.33 | 0.80, 2.22 | | 1.09 | 0.73, 1.63 | |
| **Adjuvant** | | | | 0.5 | | | 0.6 |
| **No** | 513 (69) | — | — | | — | — | |
| **Yes** | 96 (13) | 1.22 | 0.71, 2.07 | | 1.10 | 0.74, 1.65 | |
| **Histologic Subtype** | | | | 0.7 | | | 0.055 |
| **Lepidic** | 136 (18) | — | — | | — | — | |
| **Papillary/Acinar** | 441 (60) | 1.24 | 0.63, 2.44 | | 2.08 | 1.16, 3.72 | |
| **Micropapillary/Solid** | 153 (21) | 1.05 | 0.50, 2.22 | | 1.98 | 1.06, 3.69 | |
| **Unknown** | 10 (1.4) | 1.79 | 0.49, 6.64 | | 0.82 | 0.18, 3.65 | |
| **Procedure Type** | | | | 0.12 | | | <0.001 |
| **Segmentectomy** | 105 (14) | — | — | | — | — | |
| **Lobectomy** | 610 (82) | 2.15 | 0.94, 4.92 | | 2.06 | 1.11, 3.81 | |
| **Pneumo/Bilobe** | 25 (3.4) | 2.38 | 0.77, 7.39 | | 6.49 | 2.98, 14.1 | |
| **Pathologic Stage** | | | | <0.001 | | | <0.001 |
| **I** | 456 (62) | — | — | | — | — | |
| **II** | 157 (21) | 2.98 | 1.76, 5.02 | | 3.88 | 2.55, 5.89 | |
| **III** | 127 (17) | 4.13 | 2.53, 6.74 | | 8.75 | 5.96, 12.8 | |

EvW score, Elixhauser-van Walraven score; HR, Hazard Ratio; CI, Confidence Interval; MME, milligram morphine equivalents; Pneumo/bilobe, pneumonectomy/bilobectomy

# FIG. 6A

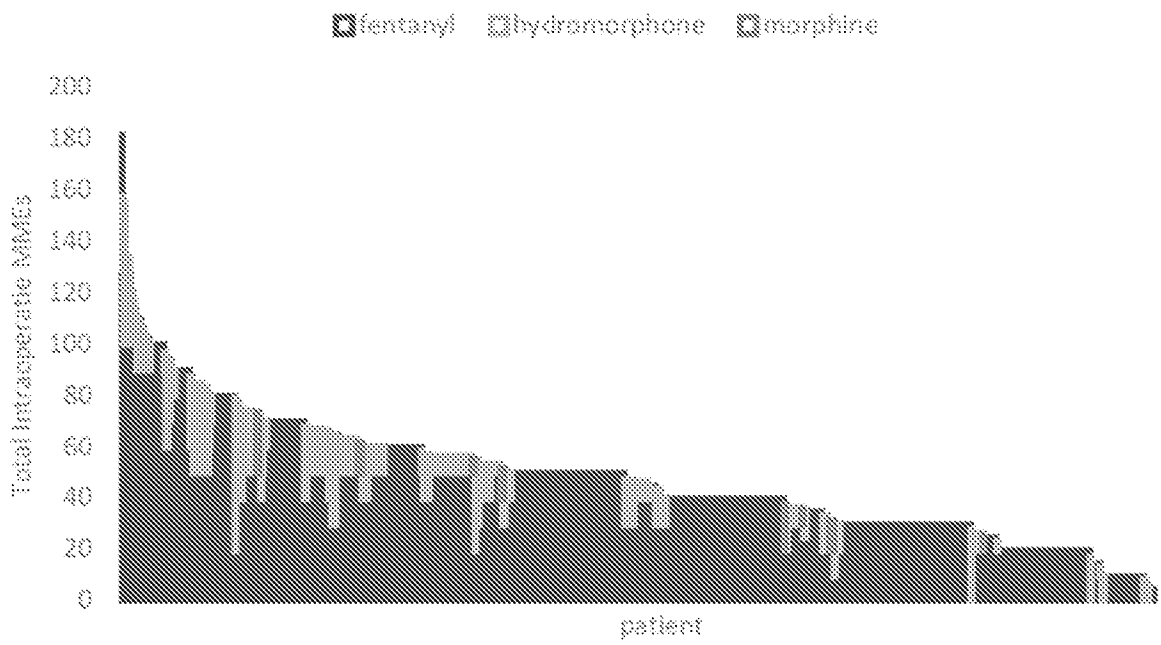
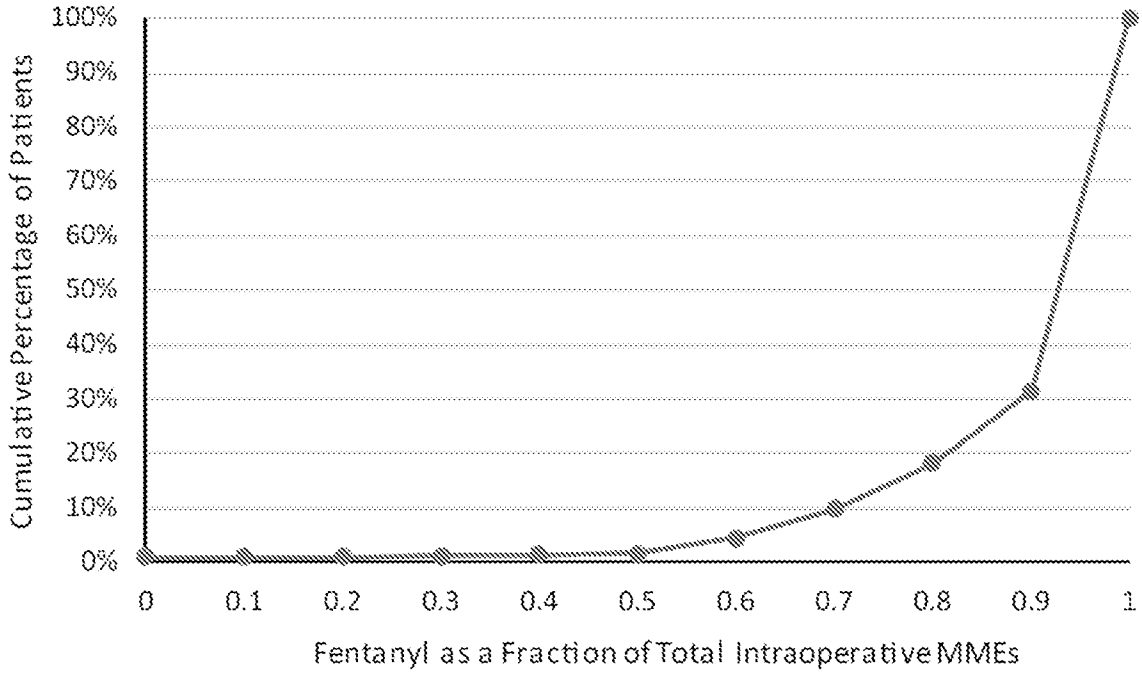

fentanyl
hydromorphone
morphine
200
180
160
140
120
100
80
60
40
20
0
Total Intraoperative MMEs
patient

**FIG. 6B**


100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
Cumulative Percentage of Patients
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
Fentanyl as a Fraction of Total Intraoperative MMEs

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 22/20497

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61P 35/00; A61K 31/135; A61K 31/137 (2022.01)

CPC - A61P 35/00; A61K 31/135; A61K 31/137; A61K 9/0019

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 2019/0175731 A1 (BIOHAVEN PHARMACEUTICAL HOLDING COMPANY), 13 June 2019 (13.06.2019), para [0016]-[0017], [0019], [0022], [0027], [0127], claims 1, 8, 18-20, 28, 30. | 1-5 |
| A | COHEN et al, 'Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain From the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists', volume 43, number 5, 01 July 2018 (01.07.2018), pg 521-546, particularly pg 521-525. | 2-5 |
| A | RZESKI et al, 'Glutamate antagonists limit tumor growth', Proceedings of the National Academy of Sciences of the United States of America, volume 98, number 11, 22 May 2001 (22.05.2001), pg 6372-6377. | 1-5 |
| A | NORTH et al, 'NMDA receptors are expressed by small-cell lung cancer and are potential targets for effective treatment', Clinical Pharmacy: Advances and Applications, volume 2, 31 March 2010 (31.03.2010), pg 31-40. | 1-5 |
| A | US 6,797,692 B1 (IKONOMIDOU), 28 September 2004 (28.09.2004), entire document. | 1-5 |
| A | US 2019/0255061 A1 (AI THERAPEUTICS), 22 August 2019 (22.08.2019), entire document. | 1-5 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"D" document cited by the applicant in the international application
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 03 May 2022 | JUN 14 2022 |
| Name and mailing address of the ISA/US<br>Mail Stop PCT, Attn: ISA/US, Commissioner for Patents<br>P.O. Box 1450, Alexandria, Virginia 22313-1450<br>Facsimile No. 571-273-8300 | Authorized officer<br>Kari Rodriquez<br>Telephone No. PCT Helpdesk: 571-272-4300 |

# INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 22/20497

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 6-28
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.