

A phase II study of pembrolizumab and paclitaxel in refractory small cell lung cancer

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Protocol History

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**Seoul National University Hospital
Internal Medicine**

Pf. Bhumsuk Keam

TRIAL SUMMARY

Study title	Phase II study of pembrolizumab and paclitaxel in refractory small cell lung cancer
Principle Investigator (PI)	Bhumsuk Keam, Seoul National University Hospital
Supporter	MSD Korea
Study centers	Seoul National University Hospital Seoul National University Bundang Hospital Seoul National University Boramae Medical Center
Study objectives	1) Primary endpoint: Response rate (RR) 2) Secondary endpoint: Progression-Free Survival (PFS), Overall Survival (OS), Toxicity.
Study design	Open, multicenter, single arm, phase II
Planned number of patients	26 Patients
Vulnerable subject	N/A
Inclusion criteria	<ul style="list-style-type: none"> 1) Have histologically or cytologically-confirmed diagnosis of small cell lung cancer 2) Extensive disease (distant metastasis, contralateral hilar lymph node involvement, or cytologically confirmed malignant pleural effusion) 3) Have had progression of SCLC following receipt of etoposide plus platinum combination chemotherapy. 4) If patients have brain metastasis with neurological symptom, they should be stabilized neurologically with prior radiotherapy or surgery for the brain metastasis (no neurologic symptom in progress and without further steroid treatment) 5) Have measurable disease based on RECIST 1.1 6) Be ≥ 20 years of age on day of signing informed consent. 7) Have a performance status of 0 or 1 on the ECOG Performance Scale 8) Have provided tissue for biomarker analysis from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion after previous

	<p>chemotherapy</p> <p>9) Demonstrate adequate organ function as</p> <ul style="list-style-type: none"> - Absolute neutrophil count 1,500 cells/mm³, platelets 100,000 cells/mm³, Hemoglobin \geq 9 g/dL - Serum creatinine \geq institutional upper normal limit (UNL) x 1.5 or GFR \geq 60 mL/min (creatinine levels $>$ 1.5 X ULN for subject with Cockcroft-Gault Equation estimated GFR \geq 60 mL/min is allowed.) - Serum transaminase \leq UNL x 2.5 (for subjects with liver metastases UNL x 5.0), Serum bilirubin \leq UNL x 1.5 <p>10) Informed consent from patient which conforms to Institutional Review Board</p> <p>11) Expected survival \geq 3 months</p>
Exclusion criteria	<p>1) Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks prior to the first dose of trial treatment.</p> <p>2) Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.</p> <p>3) Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., \leq Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.</p> <p>4) Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., \leq Grade 1 or at baseline) from adverse events due to a previously administered agent.</p> <p>Note: Subjects with \leq Grade 2 neuropathy or \leq Grade 2 alopecia are an exception to this criterion and may qualify for the study.</p> <p>Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.</p> <p>5) Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.</p> <p>6) Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by</p>

	<p>imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.</p> <p>7) Has an active autoimmune disease requiring systemic treatment within the past 2 years or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic or immunosuppressive agents. (Subjects that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement, diabetes Type I, or resolved childhood asthma/atopy will not be excluded from the study.)</p> <p>8) Has evidence of interstitial lung disease or active non-infectious pneumonitis.</p> <p>9) Has an active infection requiring systemic therapy.</p> <p>10) Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.</p> <p>11) Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.</p> <p>12) Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment. (Female and male subject of childbearing potential must use an effective barrier method of contraception during study)</p> <p>13) Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2 or anti CTLA-4 agent.</p> <p>14) Has a known history of Human Immunodeficiency Virus (HIV) (HIV-1/2 antibodies).</p> <p>15) Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected). (Inactive healthy carriers of HBV with appropriate prophylactic antiviral agents are allowed.)</p> <p>16) Has received a live virus vaccine within 30 days of planned start of trial treatment.</p> <p>17) Has a known history of active TB (Bacillus Tuberculosis)</p>
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	18) Has a history of severe hypersensitivity reaction to pembrolizumab or paclitaxel, or has a known contraindication to paclitaxel.
Planned treatment	<p>1) PD-L1 induction phase:</p> <ul style="list-style-type: none"> - Paclitaxel 175mg/m2, Day 1 q 3weeks, intravenous <p>2) Post induction treatment phase</p> <ul style="list-style-type: none"> - Paclitaxel 175mg/m2, Day 1 q 3weeks (maximum up to total 6 cycles) + Pembrolizumab 200mg D1 q 3 weeks, intravenous <p>3) Maintenance phase</p> <ul style="list-style-type: none"> - Pembrolizumab 200mg D1 q 3 weeks, intravenous till PD or unacceptable toxicity
Statistical methods	Progression free survival, Overall survival (Survival curve: Kaplan-Meier) H0 : Response rate (RR) 25% H1: RR 50%
Efficacy evaluation	RR (modified RECIST1.1), PFS, OS
Safety evaluation	NCI CTCAE version 4.0
Study period	IRB approval ~ 31 Aug 2018 Follow up : 12 months for each patient

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1. Study title and phase

1.1. Title

- 1) English : Phase II study of pembrolizumab and paclitaxel in refractory small cell lung cancer
- 2) Korean : 불응성 소세포폐암에서 Pembrolizumab 과 paclitaxel 병용 치료요법에 대한 제 2 상 임상연구

2. Study centers

Center	Address
Seoul National University Hospital	28-21, Yeongeon-dong, Jongno-gu, Seoul
Seoul National University Bundang Hospital	300, Gumi-dong, Bundang-gu, Seongnam-si, Gyeonggi-do
Seoul National University Boramae Medical Center	425, Sindaebang 2-dong, Dongjak-gu, Seoul

3. Principle investigator and Sub-investigator

3.1. Principle investigator (PI)

Seoul National University Hospital, Internal medicine
Professor, Bhumsuk Keam
Tel 02-2072-7215, FAX 02-764-7379, e-mail bhumsuk@snu.ac.kr

3.2. Sub-investigator

(Seoul National University Hospital)

Hemato-oncology Professor	Dae Seog Heo
Hemato-oncology Professor	Dong Wan Kim
Hemato-oncology Professor	Tae Min Kim

Hemato-oncology Professor	Mi So Kim
(Seoul National University Bundang Hospital)	
Hemato-oncology Professor	Jong Seok Lee
Hemato-oncology Professor	Yu Jung Kim
Hemato-oncology Professor	Se Hyun Kim
(Seoul National University Boramae Medical Center)	
Hemato-oncology Professor	Jin Soo Kim

3.3. Clinical trial pharmacists

Seoul National University Hospital, Department of Pharmacy, Hong Won Jang,
daisy0625@snuh.org, 02-2072-7439
MSD, Medical Project Associate, Mi Sung Choi, mi.sung.choi@merck.com, 02-331-2248

4. Funding agency

MSD Korea
163, Mapo-daero, Mapo-gu, Seoul

5. Planned study period

IRB approval ~ 31 Aug 2018

6. Clinical indication

Refractory SCLC, ED (Etoposide failure)

7. Background and Rationale

7.1. Background

7.1.1. Small cell lung cancer

Small cell lung cancer (SCLC) accounts for approximately 20% of lung cancer.¹ First-line treatment for patients with extensive disease, which means that the cancer had spread outside of the chest, is platinum-based combination chemotherapy. Despite 60-70 % of response rate to platinum-based combination chemotherapy, SCLC shows very poor prognosis with a median survival of less than 12 months.² While monotherapy or combination chemotherapies have been investigated in the treatment of relapsed SCLC, no standard second-line chemotherapy established. In addition, response rate for the second-line chemotherapy currently used is only 10-30 %.³ For this reason, there remain considerable unmet needs for active chemotherapeutic agent in the treatment of relapsed/refractory SCLC.

7.1.2. Pembrolizumab

The PD-1 receptor-ligand interaction is a major immune check point pathway hijacked by tumors to suppress immune control. Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a mono-therapy or in combination with other treatment modalities.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Ongoing clinical trials are being conducted in advanced melanoma, non-small cell lung cancer, a number of advanced solid tumor indications including bladder cancer. The US FDA approved pembrolizumab

for the following treatment with ipilimumab, or after treatment with ipilimumab and a BRAF inhibitor in advanced melanoma patients who carry a BRAF V600E mutation.

7.1.3. Rationale for Pembrolizumab and Paclitaxel Combination

There has been studies to investigate PD-L1 expression as a potential predictive marker of response. In KEYNOTE 001, a phase 1 study of pembrolizumab in advanced NSCLC patients, ORR was 45.4% in patients with PD-L1 expression in at least 50% of tumor cells, while ORR was 16.5% and 10.7%, respectively in patients with PD-L1 expression in 1~49% and < 1% of tumor cells.

Cytotoxic chemotherapy modulate the expression of PD-L1 on cancer cell. While doxorubicin has been reported to down-regulate PD-L1 expression on cancer cell surface, whereas paclitaxel and etoposide increase PD-L1 expression.^{5,6} Paclitaxel monotherapy showed ORR 29%, median survival time 100 days in refractory SLCL.⁷ To combine pembrolizumab with paclitaxel in etoposide failure SCLC, we expect 1) upregulation of PD-L1 expression on tumor cell, 2) tumor shrinkage by paclitaxel and 3) long duration of response by pembrolizumab.

7.2. Rationale

7.2.1. Rational for Dose selection

An open-label Phase I trial (KEYNOTE 001) is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. Two cohort evaluations of melanoma and non-small cell lung cancer (NSCLC) subjects receiving pembrolizumab at a dose of 2 mg/kg Q3W or 10 mg/kg Q2W or Q3W have been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. The rationale for a 200 mg fixed dose Q3W regimen of Pembrolizumab in this study is based on: 1) similar efficacy and safety of Pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, and

200 mg fixed dose Q3W, and current phase II or III clinical trials are being conducted with 200 mg fixed dose Q3W. 3) the lack of effect of tumor burden or indication on distribution behavior of Pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of Pembrolizumab target engagement will not vary meaningfully with tumor type.

Keynote-012 Cohorts A and C in NSCLC received paclitaxel + carboplatin + pembrolizumab (4 cycles of pembrolizumab 2 or 10 mg/kg plus carboplatin area under the time-concentration curve (AUC) 6 and paclitaxel 200 mg/m² Q3W, followed by pembrolizumab monotherapy). Except anemia and febrile neutropenia, one in the 2mg/kg group and one in the 10mg/kg group experienced treatment-related grade 3-4, and twelve in 25 patients experienced \geq grade 1 adverse event. Relationship between toxicities and pembrolizumab was not certain and most toxicities were considered due to paclitaxel plus carboplatin. Therefore, it was difficult to consider that pembrolizumab combined with chemotherapy significantly increased toxicity.⁹ Because there were no significant toxicities in this study using pembrolizumab plus paclitaxel and carboplatin, treatment-related toxicities of pembrolizumab plus paclitaxel in our study would not be considerable.

7.2.2. Rational for Efficacy Endpoints

The primary efficacy objective of this study is to evaluate the overall response rate (ORR) of MK-3475 and paclitaxel. If radiologic imaging by local/site assessment shows PD based on RECIST v1.1, tumor assessment may be repeated 4 weeks later in order to confirm PD with the option of continuing treatment per below while awaiting radiologic confirmation of progression according to modified RECIST 1.1. If repeat imaging still meets the threshold for PD (\geq 20% increase in tumor burden compared to nadir) but shows a reduction in tumor burden compared to the previous time point, treatment may be continued. If repeat imaging confirms progressive disease without reduction in tumor burden compared to the previous time point, subjects will be discontinued from study therapy. In determining whether

or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions.

Subjects who have initial evidence of radiological PD, it is at the discretion of the treating physician whether to continue a subject on study treatment until repeat imaging is obtained a minimum of 4 weeks later. This decision should be based on the clinical judgment of the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

If possible, the subject should not stop the treatment until disease progression is confirmed. This study will allow continuing treatment in subjects have initial evidence of radiological PD, because some subjects experienced transient tumor flare (pseudoprogression) within the first few months after the initiation of immunotherapy and delayed tumor response.

7.2.3. Rational for Safety Endpoints

All adverse events will be assessed by the investigator. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE criteria v4.0. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes.

7.2.4. Rational for exploratory biomarker research

Biomarker research to identify predictive factors for pembrolizumab therapy will be performed. Pre- & post- tumor, tumor at progression time and blood samples from this study will be performed. Biomarker research may undergo proteomic, genomic and transcriptional analyses. Pre- biopsy will be done before paclitaxel and post- biopsy will be done after one cycle of induction paclitaxel. After that, patients will be administered pembrolizumab and paclitaxel combination chemotherapy till progression or unacceptable toxicity. After one cycle of paclitaxel and after progression biopsy will be done in case of patient agreement. If there was clinically significant risk for biopsy (i.e. emphysema and pneumothorax), pre- and post biopsy can be waived by investigator's judgement. Blood samples will be collected at the time of **baseline and after 2cycle of paclitaxel** to carry out translational research, and tumor tissues were collected in case of patient agreement

- Tumor IHC: tumor (PD-L1, PD-L2, MHC class I), TIL (CD8, PD1, CD3, CD4), Treg (FoxP3), Macrophage (PD-L1, CD68, CD163, CD206), Spatial association of PD-1+ tumor infiltrating lymphocytes (TILs) and PD-L1+ / PD-L2+ cell.
- tumor: target gene sequencing using cancer panel
- blood sampling at baseline, after 2nd cycle, at progression(**optional**): IFN gamma quantitation, FACS - CD3+/ CD16+56+/ CD45+, CD4+, CD8+

8. Study objectives and hypothesis

This is a phase II multi-center, open-label study to evaluate efficacy and safety of paclitaxel and pembrolizumab combination treatment in patients with refractory SCLC.

8.1. Primary objective

- 1) Objective: Response rate based on RECIST 1.1
- 2) Hypothesis: Intravenous administration of pembrolizumab and paclitaxel has clinically meaningful benefit in RR

8.2. Secondary objectives

- 1) Overall Survival (OS), defined as time from first dose to death or last date of follow-up.
- 2) Progression-free Survival (PFS) base on modified RECIST 1.1
- 3) Toxicity

8.3. Exploratory objective

Biomarker analysis will be done by paired biopsy before and after induction phase and blood sampling for immune monitoring in order to find out potential predictive biomarker for pembrolizumab. Tumor tissue will be used for target gene sequencing and immunohistochemistry (IHC). Tumor IHC parameters will be include following parameters: tumor (PD-L1, PD-L2, MHC class I), TIL (CD8, PD1, CD3, CD4), Treg (FoxP3), Macrophage (PD-L1, CD68, CD163, CD206) etc.

9. Inclusion and Exclusion criteria, Planned sample size and Rationale

9.1. Inclusion criteria

- 1) Have histologically or cytologically-confirmed diagnosis of small cell lung cancer
- 2) Extensive disease (distant metastasis, contralateral hilar lymph node involvement, or cytologically confirmed malignant pleural effusion)
- 3) Have had progression of SCLC following receipt of etoposide plus platinum combination chemotherapy.

- 4) If patients have brain metastasis with neurological symptom, they should be stabilized neurologically with prior radiotherapy or surgery for the brain metastasis (no neurologic symptom in progress and without further steroid treatment)
- 5) Have measurable disease based on RECIST 1.1
- 6) Be ≥ 20 years of age on day of signing informed consent.
- 7) Have a performance status of 0 or 1 on the ECOG Performance Scale
- 8) Have provided tissue for biomarker analysis from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion after previous chemotherapy
- 9) Demonstrate adequate organ function as
 - Absolute neutrophil count $\geq 1,500$ cells/mm³, platelets $\geq 100,000$ cells/mm³, Hemoglobin ≥ 9 g/dL
 - Serum creatinine \leq Institutional upper normal limit (UNL) $\times 1.5$ or GFR ≥ 60 mL/min (creatinine levels $> 1.5 \times$ ULN for subject with Cockcroft-Gault Equation estimated GFR ≥ 60 mL/min is allowed.)
 - Serum transaminase \leq UNL $\times 2.5$ (for subjects with liver metastases \leq UNL $\times 5.0$), Serum bilirubin \leq UNL $\times 1.5$
- 10) Informed consent from patient which conforms to Institutional Review Board (IRB)
- 11) Expected survival ≥ 3 months

9.2. Exclusion criteria

- 1) Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks prior to the first dose of trial treatment.
- 2) Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

3) Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., \leq Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

4) Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., \leq Grade 1 or at baseline) from adverse events due to a previously administered agent.

Note: Subjects with \leq Grade 2 neuropathy or \leq Grade 2 alopecia are an exception to this criterion and may qualify for the study.

Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

5) Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

6) Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

7) Has an active autoimmune disease requiring systemic treatment within the past 2 years or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic or immunosuppressive agents. (Subjects that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement, diabetes Type I, or resolved childhood asthma/atopy will not be excluded from the study.)

- 8) Has evidence of interstitial lung disease or active non-infectious pneumonitis.
- 9) Has an active infection requiring systemic therapy.
- 10) Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
- 11) Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
- 12) Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment. (Female and male subject of childbearing potential must use an effective barrier method of contraception during study)
- 13) Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2 or anti-CTLA-4 agent.
- 14) Has a known history of Human Immunodeficiency Virus (HIV) (HIV-1/2 antibodies).
- 15) Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected). (Inactive healthy carriers of HBV with appropriate prophylactic antiviral agents are allowed.)
- 16) Has received a live virus vaccine within 30 days of planned start of trial treatment.
- 17) Has a known history of active TB (Bacillus Tuberculosis)
- 18) Has a history of severe hypersensitivity reaction to pembrolizumab or paclitaxel, or has a known contraindication to paclitaxel.

9.3. Planned sample size and Rationale

9.3.1. Planned sample size

Twenty-six patients will be enrolled

9.3.2. Rationale for sample size

The primary efficacy objective of this study is to evaluate RR of pembrolizumab and paclitaxel. Response evaluation will be done according to RECIST 1.1. There has been no known data of pembrolizumab and paclitaxel combination in SCLC.

- ♦ alpha = 0.05, beta = 0.20, one side
- ♦ H0: RR= 25%⁷
- ♦ H1: RR= 50%
- ♦ sample size = 23
- ♦ considering 10% drop out rate --> final sample size = 26

We assume that the null hypothesis is the RR of 25% (based on known response to paclitaxel monotherapy in refractory SCLC) versus the alternative hypothesis (H1) is the RR of least 50%. At a type 1 error (α) of 5% and power ($1-\beta$) of 80%, the study has to enroll 23 assessable patients. Considering a drop-out rate of 10%, total accrual patients will be 26.

9.4. Informed consent and Entry in to the trial

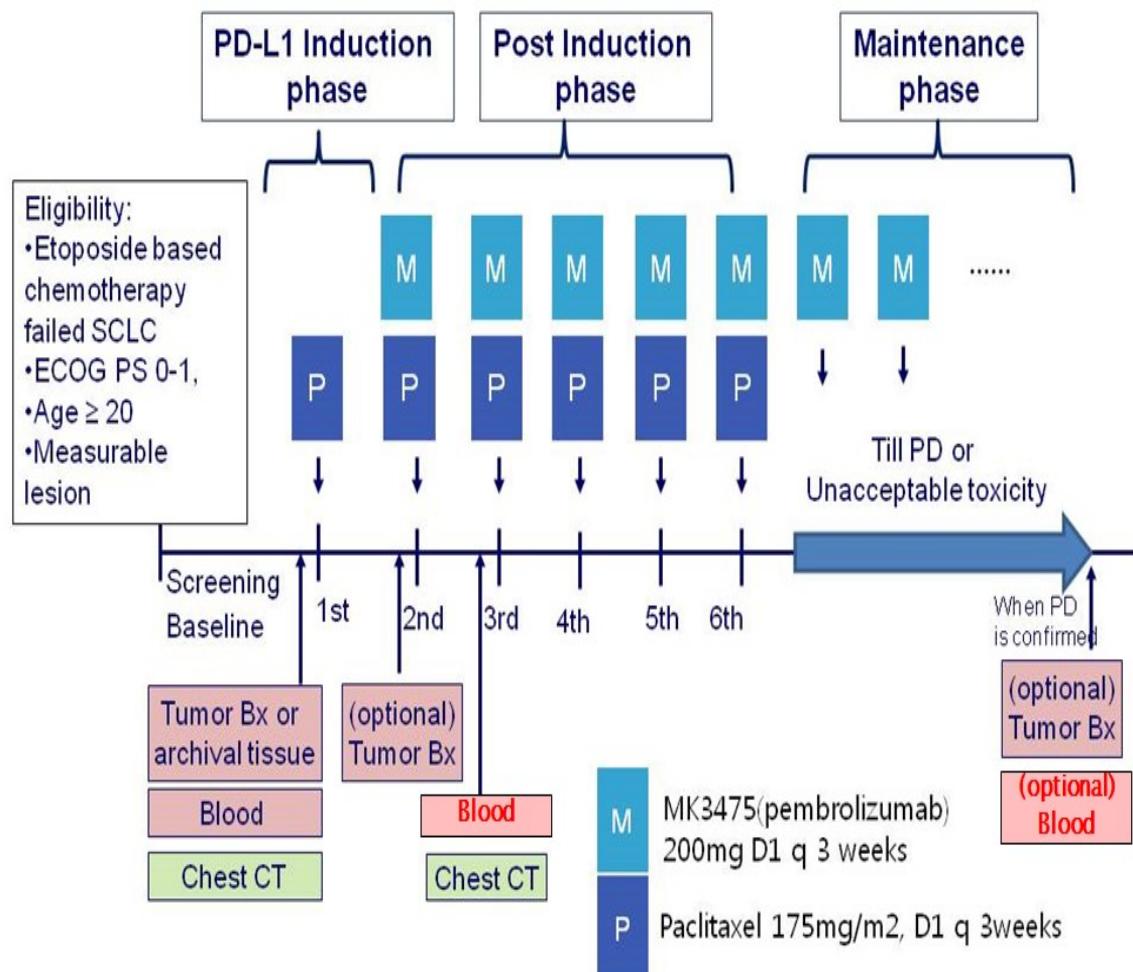
After pre-screening for subject based on the inclusion and exclusion criteria, the written informed consent from eligible subject will be obtained and subject will participate in this study.

10. Treatment plan

This study is designed to open, multi-center, single arm, phase II clinical trial. The study scheme is as follows (Figure 1).

Figure 1.

Study Scheme



10.1 Discontinuation

10.1.1 Discontinuation of Study Therapy

A subject must be discontinued from the trial for any of the following reasons before completion of planned 6 cycles.

- Radiographic disease progression (A subject may be granted an exception to continue on treatment with confirmed radiographic progression (Based on modified RECIST 1.1) if clinically stable or clinically improved)

- Unacceptable adverse events
- Pregnancy
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- The subject is lost to follow-up
- Noncompliance with trial treatment or procedure requirements

10.1.2 Early Trial Termination

If the observed results during the study indicate that continuation of the trial is unjustifiable, investigator should request for early termination of the trial to IRB, and terminate the trial by IRB approval.

- Safety of the clinical trial is greatly threatened.
 - Repeated noncompliance that causes substantial harm to subjects.
 - Increasing frequency and severity of serious adverse events specified in the protocol.
 - Missing major clinical test items than those described study protocol, informed consent form (ICF) and investigator's brochure.
- Poor enrollment of subjects making completion of the trial within an acceptable time frame unlikely.
- Although the need arises to replace the PI due to personal problems, there are no substitute investigators.
- There are serious problems with the reliability of the study site.

10.1.3 Treatment completion

- After completion of planned 6 cycles, pembrolizumab treatment may continue until confirmed PD or unacceptable adverse events if duration of response and clinical benefit from pembrolizumab is expected.

10.2 Trial treatment

Table1. Trial treatment

Drug	Dose	Dose frequency	Route of administration	Regimen/Treatment period
Paclitaxel	175mg/m ²	Q3W	IV infusion	Day 1 of each cycle
Paclitaxel + Pembrolizumab	175mg/m ² + 200mg	Q3W	IV infusion	Day 1 of each cycle
Pembrolizumab	200mg	Q3W	IV infusion	Day 1 of each cycle

10.2.1 Pembrolizumab

Trial treatment of pembrolizumab (MK-3475) should be administered on Day 1 of each 3 week cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart Pembrolizumab. Pembrolizumab (MK-3475) 200 mg will be administered as a 30 minute IV infusion every 3 weeks.

10.2.2 Paclitaxel

Trial treatment of paclitaxel should be administered on Day 1 of each 3 week cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart. Paclitaxel 175 mg/m² will be administered as an IV infusion administered over 3 hours. If the patient's body surface area (BSA) changes by more than 10% of baseline BSA (increase or decrease), it is necessary to re- calculate dose of paclitaxel. Premedications before paclitaxel include chlorpheniramine, ranitidine and dexamethasone as institutional guideline. Pembrolizumab will be given followed by paclitaxel.

10.3 Concomitant medications

10.3.1 Acceptable concomitant medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids.

10.3.2 Prohibited concomitant medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required.

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than paclitaxel and pembrolizumab
- Radiation therapy
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. (measles, mumps, rubella, varicella/zoster, and yellow fever)
- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids or corticosteroids before paclitaxel to prevent severe hypersensitivity reaction may be approved based on the investigator's judgment.

10.4. Supportive care

10.4.1 Supportive care guidelines for Pembrolizumab

- 1) Anti-infectives: Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.
- 2) Management of Infusion Reactions: Acute infusion reactions (which can include cytokine release syndrome, angioedema, or anaphylaxis) are different from allergic/hypersensitive reactions, although some of the manifestations are common to both AEs. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Signs/symptoms may include: Allergic reaction/hypersensitivity (including drug fever); Arthralgia (joint pain); Bronchospasm; Cough; Dizziness; Dyspnea (shortness of breath); Fatigue (asthenia, lethargy, malaise); Headache; Hypertension; Hypotension; Myalgia (muscle pain); Nausea; Pruritus/itching; Rash/desquamation; Rigors/chills; Sweating (diaphoresis); Tachycardia; Tumor pain (onset or exacerbation of tumor pain due to treatment); Urticaria (hives, welts, wheals); Vomiting.

Table 2. Treatment guidelines for infusion reaction to pembrolizumab

Grade	Treatment
1	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Interruption not indicated;
2	Stop Infusion and monitor symptoms. Additional appropriate medical therapy may include but is not limited to: IV fluids, Antihistamines, NSAIDS, Acetaminophen, Narcotics If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.
3/4	Stop infusion, Additional appropriate medical therapy.

	Subject is permanently discontinued from further trial treatment administration.
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10.4.2 Supportive Care Guidelines for Paclitaxel

Pre-medications for paclitaxel paclitaxel will be given as per standard of care. In order to avoid the occurrence of severe hypersensitivity reactions, all patients treated with paclitaxel should be premedicated. Subjects who experience severe hypersensitivity reactions (e.g., generalized rash/erythema, hypotension and/ bronchospasm, angioedema or anaphylaxis) should be discontinued from trial treatment.

Other supportive care includes antidiarrhea, opioid and nonopioid analgesics, appetite stimulant, granulocyte-colony stimulating factor (G-CSF), and erythropoietin. Nonpharmacologic supportive care such as intervention or transfusion also can be provided. Primary use of G-CSF for preventing neutropenia is not permitted. If grade 4 neutropenia or \geq grade 3 febrile neutropenia occurs, use of G-CSF is permitted for secondary prophylaxis according to investigator's discretion. However, G-CSF for secondary prophylaxis can be administered 24 hours after the end of paclitaxel.

10.5. Adverse events and Dose modification

10.5.1. Dose modification for Pembrolizumab

Both non-serious and serious adverse events related to exposure to pembrolizumab may have an immunologic etiology. IrAEs may be predicted based on the nature of the pembrolizumab, its mechanism of action, and reported experience with immunotherapies that have a similar mechanism of action. An irAE can occur shortly after the first dose or several months after the last dose of treatment. If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an adverse event as an irAE. Permanent discontinuation should be considered for any severe or life-threatening AEs per Table 3 below.

Table 3. Dose Modification Guidelines for Pembrolizumab

Toxicity	Grade	Timing for restarting treatment	Discontinue Subject
Diarrhea/Colitis	Grade 2,3	Toxicity resolves to Grade 0-1 or baseline	Toxicity does not resolve within 12 weeks of last infusion, or corticosteroid dosing cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks
	Grade 4	N/A	Yes
AST, ALT or Total bilirubin increase	Grade 2	Toxicity resolves to Grade 0-1 or baseline	Toxicity does not resolve within 12 weeks of last infusion
	Grade 3,4	N/A	Yes
Type 1 DM (newly developed), or hyperglycemia	T1DM or Grade 3,4	Withhold any scheduled dose of pembrolizumab until metabolic control is achieved	Once clinically and metabolically stabilized, the delayed dose of pembrolizumab may be given
Hypophysitis	Grade 2-4	Toxicity resolves to Grade 0-1 or baseline.	Toxicity does not resolve within 12 weeks of last infusion, or corticosteroid dosing cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks
Hyperthyroidism	Grade 3	Toxicity resolves to Grade 0-1 or baseline	Toxicity does not resolve within 12 weeks of last infusion, or corticosteroid dosing cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks
	Grade 4	N/A	Yes
Hypothyroidism		Hypothyroidism may be managed with replacement therapy without treatment interruption.	Hypothyroidism may be managed with replacement therapy without treatment interruption.
Infusion-related reactions	Grade 3,4	N/A	Yes

Pneumonitis	Grade 2	Toxicity resolves to Grade 0-1 or baseline	Toxicity does not resolve within 12 weeks of last infusion, or corticosteroid dosing cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks
	Grade 3-4	N/A	Yes
Nephritis	Grade 2	Toxicity resolves to Grade 0-1 or baseline	Toxicity does not resolve within 12 weeks of last infusion, or corticosteroid dosing cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks
	Grade 3-4	N/A	Yes
Others	Grade 3-4	Toxicity resolves to Grade 0-1 or baseline	Toxicity does not resolve within 12 weeks of last infusion, or corticosteroid dosing cannot be reduced to ≤ 10 mg prednisone or equivalent per day within 12 weeks
	Grade 4	N/A	Yes
Note: Subjects who experience a recurrence of the same severe or life-threatening event at the same grade or greater with rechallenge of pembrolizumab should be discontinued from trial treatment			

10.5.2. Dose modification for Paclitaxel

Subjects must have adequate organ function (Table 4) before each dose of study drug and recovered from previous treatment-related toxicities to baseline or < grade If not, treatment have to hold until recovery. The laboratory tests must be measured within 48 hours before each dose of study drug.

Table 4. Adequate Organ Function Laboratory Values

System		Laboratory value
Hematological	Absolute neutrophil count	> 1,500 cells/mm ³
	Platelets	> 100,000 cells/mm ³

	Hemoglobin	≥ 9 g/dL
Renal	Creatinine	Serum creatinine \leq institutional (UNL) \times 1.5 or Cockcroft-Gault Equation estimated GFR ≥ 60 mL/min
Liver	Transaminase (AST, ALT)	\leq UNL \times 2.5 (\leq UNL \times 5.0 for subjects with liver metastases)
	Total bilirubin	\leq UNL \times 1.5

Dose modification guidelines for paclitaxel-related adverse events are listed in Table 5.

Table 5. Paclitaxel Dose Modification for Drug-Related Adverse Events

Toxicity	Grade	Occurrence	Dose modification	Hold treatment	Discontinuation
Hematologic toxicities					
Neutropenia	Grade 1, 2, 3 or Grade 4 lasting ≤ 7 days	All	Restart treatment at Paclitaxel 135 mg/m ²	N/A	N/A
	Grade 4 lasting > 7 days	1 st & 2 nd occurrence	Restart treatment at Paclitaxel 135 mg/m ²	Hold treatment until neutrophils recover to > 1500 cells/mm ³	Treatment discontinuation should be considered
		3 rd occurrence	N/A	Yes	Yes
Febrile neutropenia		1 st occurrence	Restart treatment at Paclitaxel 135 mg/m ²	Hold treatment until neutrophils recover to > 1500 cells/mm ³	
		2 nd occurrence	Restart treatment at Paclitaxel 100 mg/m ²	Hold treatment until neutrophils recover to > 1500 cells/mm ³	
		3차	N/A	Yes	Yes

Anemia	Grade 1,2,3	All	N/A	Until anemia resolves to Grade 1 or baseline	N/A
	Grade 4	1 st & 2 nd occurrence	Restart treatment at Paclitaxel 135 mg/m ²	Until anemia resolves to Grade 1 or baseline	Treatment discontinuation should be considered
		3 rd occurrence	N/A	Yes	Yes
Thrombocytopenia	Grade 1,2,3	All	N/A	Hold treatment until platelets recover to >100,000 cells/mm ³	N/A
	Grade 4	1 st & 2 nd occurrence	Restart treatment at Paclitaxel 135 mg/m ²	Hold treatment until platelets recover to >100,000 cells/mm ³	Treatment discontinuation should be considered
		3 rd occurrence	N/A	Yes	Yes
Non-hematological toxicity					
Peripheral neuropathy	Grade 1,2		Restart treatment at Paclitaxel 135 mg/m ²	No	N/A
	Grade 3,4		N/A	Yes	Yes
Other toxicity	Grade 1,2	All	None	No	N/A
	Grade 3,4	1 st & 2 nd occurrence	Restart treatment at Paclitaxel 135 mg/m ²	Yes, until toxicity resolves to Grade 0-1 or baseline	Treatment discontinuation should be considered
		3 rd occurrence	N/A	Yes	Yes

10.6. Diet/Activity/Other Considerations

10.6.1. Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

10.6.2. Pregnancy and Contraception

Study drug may have adverse effects on a fetus in utero. Non-pregnant, non-breastfeeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive.

If a subject inadvertently becomes pregnant while on treatment with study drug, the subject will immediately be removed from the study. The study investigator will contact the subject and document the subject's status until the pregnancy has been completed or terminated. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the investigator.

10.6.3. Using in Nursing women

It is unknown whether MK 3475 is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

11. Assessment and Follow-up

11.1. Pretreatment evaluation

Screening procedures are to be completed within 28 days prior to the first dose of trial treatment.

Table 6. Pretreatment evaluation

		Period
Informed consent		Prior to participating in a clinical trial
Diagnosis of cancer	Date of diagnosis, Diagnosis, stage, Prior treatment for SCLC	Within 28 days
Past medical history and physical exam	Past medical history Physical exam – Vital sign, Height, Weight, Body temperature, Neurologic exam, ECOG performance status, Electrocardiogram, Chest X-ray	Within 28 days
Hematology	WBC, Absolute neutrophil count, Platelet count, Hemoglobin	Within 28 days
Chemistry	Albumin, Glucose, Alkaline phosphatase, Transaminase (AST, ALT), Total bilirubin, Creatinine, Electrolyte (Na, K, Mg), Calcium, phosphorus	Within 28 days
Serology	HBsAg, HCV Ab, HIV Ab	Within 28 days
Coagulation	PT, aPTT, INR	Within 28 days
Thyroid function test	free T4, TSH	Within 28 days
Urinalysis	pH, blood, glucose, albumin, Microscopic exam, if abnormal results are noted	Within 28 days
Blood sampling	IFN gamma quantitation, FACS- CD+/CD16+56+/ CD45+, CD4+, CD8+	Within 28 days
Tumor biopsy	IHC: Spatial association of PD-1+ tumor infiltrating lymphocytes (TILs), PD-L1+ cells, PD-L2+ (tumor and myeloid cells 등	Archival tissue
Tumor imaging	Chest CT Abdomen-Pelvis CT (If necessary,)	Within 28 days
Pregnancy test	Perform on women of childbearing potential only. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test (HCG) will be required. (age \geq 60 years or amenorrhea lasting 12 or more months is considered postmenopausal.)	Within 72 hours

Other	If clinically required	Within 28 days
Concomitant Medications	record prior medication taken by the subject within 30 days before starting the trial	Within 28 days

*For serology, the previous test results may be used.

11.2. Assessment during treatment

All subjects will be evaluated according to the following schedule

Table 7. Assessment during treatment

		Period
Physical exam	Vital sign, Height, Weight, Body temperature, ECOG performance status, Chest X-ray	Within 3 days prior to Day 1 of each cycle
Hematology	WBC, Absolute neutrophil count, Platelet count, Hemoglobin	Within 3 days prior to Day 1 of each cycle
Chemistry	Albumin, Glucose, Alkaline phosphatase, Transaminase (AST, ALT), Total bilirubin, Creatinine, Electrolyte (Na, K, Mg), Calcium, phosphorus	Within 3 days prior to Day 1 of each cycle
Urinalysis	pH, blood, glucose, albumin, Microscopic exam, if abnormal results are noted	Within 3 days prior to Day 1 of each cycle
Thyroid function test	free T4, TSH	Within 3 days prior to Day 1 of each cycle
Tumor assessment	Physical exam	Every visits
	Chest CT	Day 14-21 of each 2-cycle (each 3-cycles, after completion of 6 cycles)
	Abdomen-pelvis CT (if necessary)	Day 14-21 of each 2-cycle (each 3-cycles, after completion of 6 cycles)
Others	If clinically required	
Concomitant Medications	record newly or added medication taken by the subject	Every visits

AEs	Record most severe NCI CTCAE v.4.0 grade on CRF	Within 3 days prior to Day 1 of each cycle
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* A blood sample: after 2 cycle, disease progression (optional)

* Tumor tissue : 1cycle After (optional) , disease progression(optional)

11.3.Follow up

Patients will be followed for 3 weeks after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

12. Assessment

12.1.Safety Assessment

Safety will be assessed for all subjects and documented according to the CTCAE v4.0 Common Terminology Criteria for Adverse Events (CTCAE). Results that meet the criteria for serious adverse events or are considered clinically meaningful should be reported and recorded terms and severity of adverse events on CRF according to CTCAE v4.0.

12.2.Efficacy Assessment

Tumor response will be assessed based on modified RECIST 1.1, according to planned schedule. All lesions (measurable, evaluable, non-evaluable) must be recorded. Assessment of tumor response must be carried out in the same way during study period. The planned schedule of assessment is as follows;

- Day 14-21 of every 2 cycle during 6 cycles of pembrolizumab plus paclitaxel. (If treatment is delayed, assessment should be done before the start of next cycle.) Then, day 14-21 of every 3 cycles after 7 cycles of pembrolizumab monotherapy.
- At the time of suspected disease progression

12.2.1. Response Rate (RR)

Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Response rate will be evaluated based on RECIST 1.1 in order to account for the unique tumor response profile. PFS and ORR per modified RECIST 1.1 are defined as specified for the respective endpoints using RECIST 1.1, with the exception that a confirmation assessment of PD (at least 4 weeks after the initial PD assessment) is required for subjects who remain on treatment following a documented PD per RECIST 1.1. Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration". Every effort should be made to document the objective progression even after discontinuation of treatment.

12.2.2. Progression Free Survival (PFS)

PFS is the secondary objective of this study. PFS is defined as the time from first dose to disease progression or death due to any cause. Disease progression is assessed by modified RECIST 1.1. Subjects with no documented progression or death will be censored at the last date at which they are known to have no progression. Patients lacking an evaluation of disease after first study treatment will have their PFS time censored on the date of first dose with duration of 1 day. Date of the first assessment at which PD is objectively documented will be used for PFS analysis,

although PD is confirmed in subsequent tumor assessments. The Kaplan-Meier method will be used to estimate the survival curves and median time and confidence interval will also be reported.

12.2.3. Overall Survival (OS)

Overall Survival is defined as the time from first dose to death due to any cause. Through the follow-up within 30 days after study completion or termination of the last subject, death and date of death will be checked for subject alive during treatment period. Patients without documented death at the time of the final analysis will be censored at the date of the last follow-up. The Kaplan-Meier method will be used to estimate the survival curves and median time and confidence interval will also be reported.

13. Subject registration

Eligible subjects have to be registered before start of treatment. Subjects will be competitively enrolled at multiple centers sites. Seoul National University Bundang Hospital and Seoul National University Boramae Medical Center are participating centers. Registration will be done to enter subject information on eCRF. Subjects will be given a three-digit institution number and a three-digit subject number.

14. Adverse event

14.1. Definition

- 1) Adverse Event (AE) : Any untoward or unfavorable medical occurrence in a human study participant, including any abnormal sign (e.g. abnormal physical exam or laboratory finding), symptom, or disease, whether or not considered related to participation in the research.

2) Adverse Drug reaction (ADR):

"Adverse Drug Reaction (ADR)" : Any response to study drug which is noxious and unintended, and which occurs at doses normally used in human. The causal relationship between study drug and the adverse event cannot be excluded.

3) A serious adverse event (SAE/ADR) is any adverse event occurring at any dose or during any use of study drug that:

- Results in death; Is life threatening;
- Results in or prolongs an existing inpatient hospitalization;
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect;
- Is another important medical event

However, following events should not be considered as SAEs

- A hospitalization/prolonged hospitalization for treatment related to a pre-existing condition
- A hospitalization/prolonged hospitalization due to evaluate the tumor assessment
- A hospitalization/prolonged hospitalization for pre-planned treatment
- The admission results in a hospital (or an emergency room) stay of less than 24 hours
- **Admission due to disease progression**
-

4) Unexpected Adverse Drug Reaction : an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Clinical trials instruction manual or product labeling).

14.2. Evaluating and Recording Adverse Events

An investigator will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. For any AEs not listed in CTCAE v4.0, medical terms describing symptoms or signs observed by investigator or reported by subject will be recorded, according to the appropriated grading of the general definition (Table 8) .

Table 8. Evaluating Adverse Events

Grade 1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate	minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
Grade 3	Severe	Life threatening consequences; urgent intervention indicated.
Grade 4	Life-threatening or Disabling Adverse Event	Life threatening consequences; urgent intervention indicated.
Grade 5	Death	Death related to AE

14.3. Causality assessment

The causality relationship of study drug to the adverse event will be assessed by the investigator as either: Related or Not related

The following criteria should be considered in order to assess the relationship as "related":

Reasonable temporal association with drug administration

Known response pattern to suspected drug

Disappearance or decrease on cessation or reduction in dose

Reappearance on re-challenge

The following criteria should be considered in order to assess the relationship as "not related":

It does not follow a reasonable temporal sequence from administration of the drug.

It may readily have been produced by the patient's clinical state, environmental, or toxic factors, or other modes of therapy administered to the patient.

It does not reappear or worsen when the drug is re-administered.

If investigator's final decision on a causal relationship is not clear, or if investigator does not exactly know the cause of the adverse event, the adverse event considered likely related to study drug. If the investigator's causality assessment is "unknown but not related to study drug," this should be recorded in the CRF as "not related."

14.4. Adverse events reporting

14.4.1. Reporting non-serious adverse event

Information about all AEs is collected and recorded on the Adverse Event report form. Any AEs experienced after 30 days after the patient has stopped study treatment should only be reported if the investigator suspects a causal relationship to the study drug.

14.4.2. Reporting serious adverse event

Any clinical AE or abnormal laboratory test value that is serious (as defined in section 14.1 above) and which occurs during or after the course of the study, regardless of the treatment arm must be reported to IRB. In the event of any new SAE occurring, the investigator should immediately inform IRB and SAE report form

will be submitted to IRB. Immediate and follow-up reporting specify the subject using an assigned code.

Seoul National University Hospital

Kimseunghee: kshsh8@naver.com

Merck Global Safety

Fax: 215-993-1220

14.4.3. Reporting death

Deaths occurred within study period and within 30 days of last administration of study drug should be reported within 24 hours, regardless of the relevance of the study. Deaths that occur within the follow-up period and may be relevant to the study should be documented in the SAE form. All deaths, regardless of causes, should be recorded in the death CRF.

14.5. Monitoring of Subject with Adverse events

All adverse events (and their treatments) should be recorded during the treatment phase of the study and for 30 days after the administration of the final dose, and the patient should be followed up until the adverse event is resolved or until the pertinent explanation is available even after the subject completes the administration of study drug. Unrelated, mild or moderated adverse events will be followed up for 30 days after the administration of the final dose. Subjects with severe, life-threatening or related adverse events should be followed up until the adverse event is resolved, death occurs, new chemotherapy is started or the causal relationship is re-evaluated.

15. Statistical Consideration

15.1. Definition of analysis population

- Intention-To-Treatment (ITT) population will comprise all subjects who receive at least one dose of study treatment (one dose of paclitaxel in cycle 1) and who have measurable lesion at baseline. The ITT population will serve as the efficacy analysis population in this study.
- Per-protocol(PP) population will include all ITT subjects who completed the full course of assigned treatment and who do not have major protocol violations.

Efficacy will be assessed mainly in ITT population and PP population will be employed for supplementary analyses.

- The Safety analysis will be conducted for all subjects who receive at least one dose of study treatment.

15.2. Statistical analysis

A one-sided test at the 5% significance level for primary efficacy analysis and a two-sided test at the 5% significance level for other statistical analysis will be used. In addition, number of observations, mean, standard deviation, median, minimum and maximum values for continuous variables will be presented. Frequency and ratio for categorical variables will be presented.

- Primary end point: Calculate response rate and estimate the one-sided 95% confidence interval
- Secondary end point: Survival Curves using Kaplan-Meier method, Multivariate analysis using Cox proportional hazard regression model.
- Safety endpoint: Estimated frequency of treatment-related toxicities, especially a frequency of 5 percent or grade 3-4.

16. Biomarker assessment

Informed consent for specimens be obtained during screening for protocol enrollment from all subjects or legally acceptable representative, at a trial visit by the investigator or designate. Pretreatment blood sampling and tumor biopsies will be done. After one cycle of paclitaxel, blood sampling and tumor biopsies will be performed for translational research by investigator's discretion. Archival tissue obtained from the patients before the administration of study drug may also be used. Biomarker assessment before the administration of study drug will be performed at Seoul National University (SNU) Cancer Research Institute and QualTek, and later assessment will be performed at SNU Cancer Research Institute. Results of genetic test will be used for research purpose only, personal information will be protected. All specimens will be destroyed after storage for 5 years. Subjects may withdraw their consent and have their specimens and all derivatives destroyed.

17. Policy and procedures for the protection of human subjects

17.1. Ethical Aspects

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in compliance with the relevant law in Korea (the pharmaceutical affairs law, Medical Appliances Act, Bioethics and Safety Act, and relevant Korea FDA Notification) and International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use-Good Clinical Practice (ICH GCP). Prior to commencement of this study, this trial protocol will be approved by Ministry of Food and Drug Safety (MFDS) and IRB, and amendment to the study will also be approved by MFDS and IRB.

17.2. Subject Consent

The initial assessment is conducted within 28 days before the start of treatment, and subject should read and sign the ICF approved by IRB before study procedures. It is the responsibility of the investigator to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, objectives and potential hazards of the study. It must also be explained to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason. Subjects should be given a period of time to understand the study and contemplate their decision before signing a consent document. The subject's written informed consent to participate in the trial must be given before any trial-related activities are carried out. Investigator and subject or legally acceptable representative. Investigator or designee and subject should sign and date the consent form. The original signed and dated ICF will be kept at the study site and copy will be provided to subjects. A copy of the signed and dated ICF should be given to the subject before participation in the trial. If the subject or legally acceptable representative is unable to read, a reliable and independent witness should be present during the entire informed consent discussion. The choice of the witness must not breach the subject's right to confidentiality. A reliable independent witness is defined as one not affiliated with the institution or engaged in the investigation. A family member or acquaintance is an appropriate independent witness. After the subject or legally acceptable representative orally consents and has signed, if capable, the witness should sign and personally date the consent form attesting that the information is accurate and that the subject or legally acceptable representative has fully understood the content of the informed consent agreement and is giving true informed consent.

17.3. Subject Protection/Safety

Each study sites should provide specialized personnel and adequate facilities to

conduct the clinical trial in accordance with the protocol and to protect subjects. Clinical trial personnel should understand adverse events and precautions described in the protocol, stop the study in case of SAE, take appropriate management measures and inform IRB and all investigators. Every effort should be made to treat adverse event and recover from side effects. In case of hospitalization due to the study drug, effort should be made to minimize the burden on the subject. For these reasons, insurance coverage will be provided for each sites participating to the trial. Investigator will inform the review of safety information every 6 months

17.4. Confidentiality of Subject information

All information generated in this study will be considered confidential, and confidentiality of subjects will be maintained in case of publishing results of this study. All study-related documents will be kept as classified documents in a facility with regulation, and the subject will be identified by unique code only. By signing this protocol, the investigator agrees that IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process.

17.5. Records retention

The Investigator should keep all study-related documents (CRF, ICF, clinical result report, study drug administration form and the relevant information form etc.) for 3 years from the IRB approval date of study completion report.

17.6. Clinical Trials Monitoring

During the clinical trials, monitors designated by PI will carry out monitoring ethically and scientifically according to GCP guidelines. Monitoring includes reviewing study-

related documents (ICF, CRF data etc.) and verifying compliance to study protocol

18. Storage and Disposal of human biospecimens

Human biospecimens collected for exploratory biomarker research will be stored at SNU Cancer Research Institute and QualTek until 5 years after the completion of this study. Collected human biospecimens will be kept under strict control in accordance with SOP for SNU cancer research institute storage facility and storage/disposal procedures which Merck request to QualTek. When human biospecimens are stored, encrypted serial numbers will be assigned to subjects to conceal personal identification information (personal details, medical record number, name, and resident registration number) and guarantee anonymity. In case of QualTek, information will be encrypted and stored in compliance with U.S. privacy laws. Examination report and results, and the agreement is preserved for three years, and human biospecimens will be disposed immediately after the end of the storage period.

19. References

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