Precision Biotechnology

Protocol Version: PB-2018-V12

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Clinical Trial Protocol

Phase I, open-label study to evaluate safety and tolerability of PB101 in combination with standard treatment, EGFR-TKI, in EGFR-mutated advanced non-small cell lung cancer

Investigational Product Name: PB101 Autologous Immune Cell Therapy

Indication: Patients with histologically confirmed EGFR-mutated stage III/IV NSCLC

Study Type: Phase I, single-center, single-arm, open-label study

Protocol ID: PB-2018

Planned Study Start Date: September 2018

Planned Study Early Termination Date: August 2019

Study Completion Date: December 2023

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Protocol Synopsis (Cell Therapy)

Ⅰ. Protocol title:

A Phase I, open-label study to evaluate safety and tolerability of PB101 in combination with standard treatment, EGFR-TKI, in EGFR-mutated advanced non-small cell lung cancer

Ⅱ. Objectives:

To determine the safety and tolerability of PB101 in combination with standard of care EGFR-TKI in patients with EGFR-mutated advanced non-small cell lung cancer.

Ⅲ. Test Product:

1. Name: PB101
2. Cell type: NK /NKT Cell
3. Sources: ■autologous □allogeneic □homologous use □minimal manipulation

Dose(s): two-dose level: $1x10^{9*}$cells (*allow ± 10% cell number)

4. Dosing schedule: administrative route: intravenous
5. frequency: PB101 infusion weekly for 4 weeks

Ⅳ. Developmental phase: phase ■ Ⅰ □ Ⅱ □ Ⅲ □ Ⅳ □Others □First-in-human trial

Ⅴ. Study design:

1. □Control: □placebo
□active (please specify name and dosage)
□other
■Uncontrolled

2. Blinding: ■open-label □evaluator blind □single blind □double blind □double dummy □ other

3. Randomized: □yes ■no

4. □Parallel □Cross-over ■Other

5. Duration of treatment: 4 weeks

6. Titration: □forced □optional ■none

7. □Multi-national ■Multi-center(Taiwan) □Single center

Ⅵ. Endpoints

1. Primary endpoint(s):

1.1 Safety (Phase I) – to determine the dose of PB101 that can be given within dose-limiting toxicities.

2. Secondary endpoints:
To observe the overall response rate (ORR), duration of response (DR) and progression-free survival (PFS).

Ⅶ. Selection criteria:

1. Main inclusion criteria:

1.1 Men and women 20 years of age or older.
1.2 Subjects with histologically or cytologically confirmed stage IIIB/IV non-small cell lung cancer, not amenable to definitive multi-modality therapy, or recurrent disease after a prior diagnosis of stage I-III disease. All staging is via the American Joint Committee on Cancer (AJCC)/IASLC 7th edition proposed staging criteria.
1.3 EGFR sensitizing mutation must be detected in tumor tissue. Specifically, patients harboring the most common mutations, deletions in exon 19 or the L858R mutation in exon 21 are eligible. Other EGFR sensitizing mutations may be eligible after discussion with the principal investigator.
1.4 Subjects must have measurable or evaluable disease according to RECIST v1.1.
1.5 Patients may have had a prior EGFR-TKI including gefitinib, erlotinib, afatinib, or osimertinib in the metastatic setting, but treatment duration must have been less than three months at the time of enrollment.
1.6. Patients may have had no more than one prior line of chemotherapy or immunotherapy in the metastatic setting. At least 14 days must have elapsed from the last chemo/immunotherapy administration until the start of protocol treatment, and patients must have recovered from the side effects of any of these agents.
1.7 Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.
1.8 Acceptable organ function, as evidenced by the following laboratory data:
(1). Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3.0 x upper limit of normal (ULN). (for patients with known hepatic metastases, AST and/or ALT <5x ULN)
(2). Total serum bilirubin ≤1.5 x ULN
(3). Absolute neutrophil count (ANC) ≥1500 cells/mm^3
(4). Platelet count ≥75,000 cells/mm^3
(5). Hgb ≥ 10.0 g/dL
(6). Serum creatinine levels ≤1.5 * ULN, or calculated (by Cockcroft-Gault formula or other accepted formula) or measure creatinine clearance ≥50 mL/min.

2. Main exclusion criteria:

2.1. Patients with history of clinically significant interstitial lung disease or radiation pneumonitis.
2.2. Patients with brain metastasis or leptomeningeal disease.
2.3. Patients who have had radiation to the lung fields within four weeks of starting treatment. For all palliative radiation to all other sites, at least 7 days must have elapsed prior to starting to treatment.
2.4. Patients who have had major surgery (e.g., intra-thoracic, intra-abdominal or intra-pelvic) within two weeks prior to starting study drug or who have not recovered from side effects of such procedure. Video-assisted thoracic surgery (VATS) and mediastinoscopy will not be counted as major surgery and patients can be enrolled in the study ≥1 week after the procedure.
2.5 Patients with a second, clinically active, cancer. Patients with second cancers which have been treated with

curative intent and/or are currently inactive are allowed.

2.6. Known history of human immunodeficiency virus (HIV) seropositivity.

2.7. Participants who are receiving any other investigational agents. Patients previously treated with investigational agents must complete a washout period of at least one week or five half-lives, whichever is longer, before starting treatment.

2.8. Patients receiving concomitant immunosuppressive agents or chronic corticosteroid use, except those on topical or inhaled steroids, or steroids given via local injection.

2.9. Patients with clinically significant, uncontrolled cardiovascular disease, such as: unstable angina or myocardial infarction within 6 months prior to screening, abnormal left ventricular ejection fraction (LVEF <50%), cardiac arrhythmia not controlled with medication, uncontrolled hypertension defined as a SBP ≥ 160mm Hg and/or DBP ≥ 100mm Hg, with or without anti-hypertensive medication. Initiation or adjustment of antihypertensive medication(s) is allowed prior to screening.

2.10. Presence of fungal, bacterial, viral, or other infection requiring IV antimicrobials for management.

2.11 Pregnancy and lactating women.

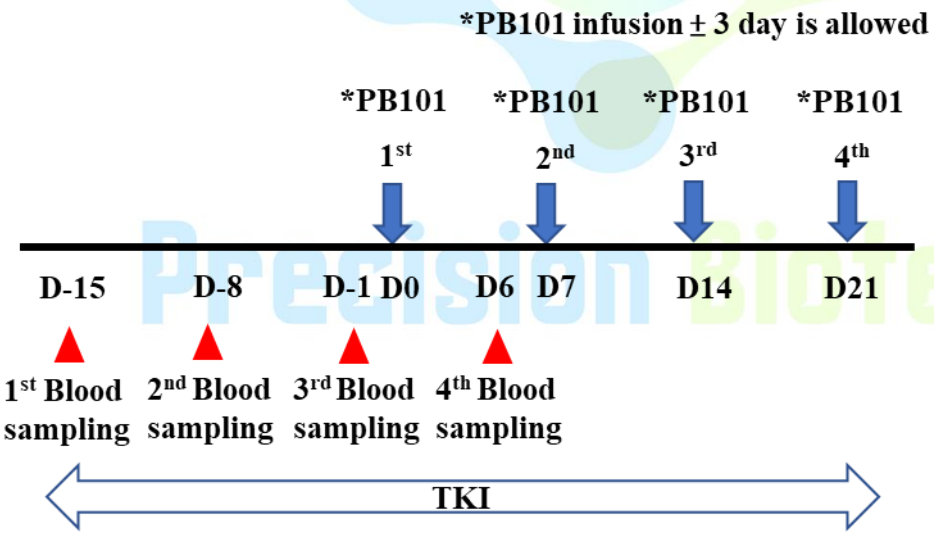
2.12 Active hepatitis B or C without treatment.

2.13. Other situations the investigators think not eligible for participation in the research.

Ⅷ. Study procedures:

This study will be conducted in one phase. Phase I will investigate safety of PB101. Subjects will be administered $1x10^{9*}$cells (*allow ± 10% cell number) of PB101 over at least 30 minutes weekly for 4 weeks via intravenous infusions, 6 patients will be evaluated. Briefly, after re-visiting to the hospital in 7±3 days to confirm the safety, the subject will continue to be given $1x10^{9}$ cells of PB101 for the following four consecutive weeks.

The schema of PB101 infusion in phase I as shown:



Ⅸ. Concomitant treatment:

1. Permitted:

1.1 Standard of care EGFR-TKIs: Gefitinib (Iressa), Erlotinib (Tarceva), Afatinib (Giotrif), or Osimertinib (Tagrisso)

2. Prohibited:

2.1 There is no absolute contraindication for concomitant medication. However, drugs affecting Iressa, Tarceva, Giotrif or Tagrisso exposure should be noticed.

2.2 Strong inducers of CYP3A4 (e.g., rifampicin, phenytoin, or tricyclic antidepressant) increase the metabolism of Iressa/Tarceva and decrease Iressa/Tarceva plasma concentrations. Increase Iressa or Tarceva daily dose in patients receiving a strong CYP3A4 inducer and resume to standard dose 7 days after discontinuation of the strong inducer.

2.3 Strong inhibitors of CYP3A4 (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO), voriconazole, or grapefruit or grapefruit juice) decrease Iressa/Tarceva metabolism and increase Iressa/Tarceva plasma concentrations. A dose reduction should be considered if severe adverse reactions occur.

2.4 Strong CYP3A4 inducer decrease the exposure of Osimertinib and may lead to reduce efficacy of Osimertinib. Avoid coadminstering Tagrisso with strong CYP3A4 inducers (e.g., phenytoin, rifampin, carbamazepine, St. John's Wort) [note: effect of St. John's Wort varies widely and is preparation dependent]. Increase the Tagrisso dosage when coadministering with a strong CYP3A4 inducer if concurrent use is unavoidable. No dose adjustments are required when Tagrisso is used with moderate and/or weak CYP3A inducers.

2.5 Drugs that elevate gastric pH (e.g., proton pump inhibitors, histamine H2-receptor antagonists, and antacids) may reduce plasma concentrations of Iressa/Tarceva. Avoid concomitant use with proton pump inhibitors, if possible. If treatment with a proton-pump inhibitor is required, take Iressa/Tarceva 12 hours after the last dose or 12 hours before the next dose of the proton-pump inhibitor. Take Iressa/Tarceva 6 hours after or 6 hours before an H2-receptor antagonist or an antacid.

2.6 International Normalized Ratio (INR) elevations and/or hemorrhage have been reported in some patients taking warfarin while on Iressa therapy. Patients taking warfarin should be monitored regularly for changes in prothrombin time or INR.

2.7 Concomitant taking of P-gp inhibitors with Giotrif can increase exposure to afatinib. Reduce Giotrif by 10 mg per day if not tolerated. Co-administration of chronic P-gp inducers orally can decrease afatinib exposure. Increase Giotrif by 10 mg per day as tolerated.

Ⅹ. Statistics:

1. Primary hypothesis: ☐superiority ☐non-inferiority ☐equivalence ■other

2. Sample size: 6 evaluable subjects

3. Efficacy population: ☐ITT ■PP ☐other
Safety population: ☐ITT ■PP ☐other

4. Statistical method(s) for efficacy/safety evaluations:

In this Phase I trial, $1x10^9$ cells/dose of PB101 will be administered to 6 patients. The incidence of DLT events in patients was recorded, and the incidence of DLT would be less than 33% (DLT is defined as the

occurrence of grade ≥ 3 (CTCAE 5.0) adverse reaction related to cell infusion). The observation time of DLT is 28 days after completion of the last PB101 infusion.

5. Planned interim analysis: ☐yes ■no

XI . Please attach flow chart and/or assessment schedule, if available.

Schedule	Day < -15	Day-15 (±3)	Day -8 (±3)	Day -1 (±3)	Day 0 (±3)	Day 6 (±3)	Day 7 (±3)	Day 14 (±3)	Day21 (±3)	Day+28 /End of Treatment/ Withdrawal	Monthly follow up
Informed Consent	V										
Medical/Oncologic History	V										
Physical Examination	V	V	V	V	V	V	V	V	V	V	V
Baseline Signs/Symptoms	V	V	V	V	V	V	V	V	V	V	V
ECOG/body weight/vital signs	V	V	V	V	V	V	V	V	V	V	V
Urinalysis	V										
CBC/DC	V		V	V	V	V	V	V	V	V	V
Blood Chemistry (GOT, GPT, BUN, T-Bil, Cr, UA, Na, K, Ca, Alb)	V				V		V	V	V	V	V
Coagulation (PT,APTT)	V				V						
Tumor markers (CEA)	V				V					V	V
Thyroid function (TSH, fT4)	V				V			V		V	
Pregnancy Test (Urine)	V										
HIV Test (ELISA)	V										
12-lead ECG	V				V			V		V	
Heart echocardiography	V									V	
Bone scan (OPTIONAL)	V										
Tumor imaging (CT or MRI)	V									V	V*
Tumor Assessments (RECIST1.1)	V									V	V*
PBMC harvest		V	V	V		V					
Cell infusion					V		V	V	V		
Adverse effect evaluation (CTCAE)	V	V	V	V	V	V	V	V	V	V	V
Case report form	01	02	03	04	05	06	07	08	09	10	11, 12

*Done on CRF12