Phase 2 study of pembrolizumab (Pemb) plus plinabulin (Plin) and docetaxel (Doc) for patients with metastatic NSCLC after failure on first-line immune checkpoint inhibitor alone or combination therapy: updated efficacy and safety results on immune re-sensitization

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Clinical trial registration: NCT05599789

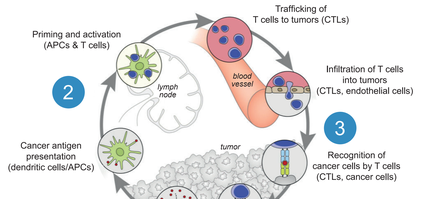
Background and Aim

(2) Plinabulin

Improved antigen presentation
Stimulate maturation of dendritic cells to increase antigen presentation[2]

(1) Radiation or Chemotherapy

Release tumor antigens
For more potent anti-cancer effect[2]



(3) Checkpoint Inhibitors

Anti-tumor T cell activation
Optimize T cell response

Figure adapted from Mellman et al. 2023.[1]
APC, antigen presenting cell; CTL, cytotoxic T lymphocyte.

- Immune checkpoint inhibitor (ICI)-based treatment regimens have become the standard of care for first-line treatment of non-small cell lung cancer (NSCLC).
  - Almost 60% patients will progress after ICI; once progressed, it is not recommended to continue ICI monotherapy, and the effect of chemotherapy is limited (overall response rate [ORR] ~10% with docetaxel, mPFS [median progression free survival] 3–4 months).[2] Therefore, there is a high unmet need.
- Plinabulin (BPI-2358) is a selective immunomodulating microtubule-binding agent that promotes dendritic cell maturation, enhances anti-tumor T cell response, and has the potential to overcome immunotherapy resistance.[3–5]
- KeyPemls-004 (303 study) is a phase 2 study aiming to evaluate the efficacy and safety of pembrolizumab (Pemb) plus plinabulin (Plin) and docetaxel (Doc) in patients with metastatic NSCLC who had progressed after ICI.

Methods and Materials

- In this investigator-initiated, single-arm, open-label, phase 2 trial, patients with metastatic NSCLC who acquired resistance after immunotherapy alone or in combination with platinum-doublet chemotherapy were enrolled.
- The ongoing study intends to enroll a total of 47 patients. Here we report an interim analysis of data from the first 30 patients enrolled.

Inclusion criteria

- Metastatic NSCLC
- Progression after ICI alone or ICI with platinum-doublet chemotherapy
- Previous PFS >6 months
- ECOG PS 0–1
- No prior docetaxel or plinabulin therapy
- No interstitial lung disease or pneumonitis requiring steroids
- EGFR-, ALK- or ROS1-directed therapy not indicated as primary treatment
- No active central nervous system metastases and/or carcinomatous meningitis

Treatment

- Pembrolizumab 200 mg IV D1 Q3W (up to 35 cycles)
- Plinabulin 30 mg/m^2 IV D1 Q3W (up to 35 cycles)
- Docetaxel 75 mg/m^2 IV D1 Q3W (up to 6 cycles)
- Up to disease progression, intolerable toxicity, or investigator decision to discontinue the drug

Endpoints

- Primary endpoint:
  - ORR per RECIST 1.1
- Secondary endpoints:
  - PFS per RECIST 1.1
  - OS
  - DoR per RECIST 1.1
  - Yearly OS-rate
  - Safety and tolerability

Stage 1: Planned enrolment: 19 patients. If ≤2 patients experienced objective response, the trial would be terminated in advance; if the number of objective responses is >2, the trial will enter Stage 2.
Stage 2: Planned enrolment: 47 patients. If >8 patients experience objective responses, the trial is considered to have reached its intended endpoint.

ALK, anaplastic lymphoma kinase; D, day; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; ICI, immune checkpoint inhibitor; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumours; ROS1, proto-oncogene tyrosine-protein kinase.

Results

- At the database lock on 29 August 2024, 36 patients were enrolled and 30 were evaluable.
- Baseline clinical characteristics are displayed in Table 1.
- Median follow-up was 11.5 months, and median age was 68.0 (range 50–77 years). Of the 30 evaluable patients, 73.3% were male and 26.7% were female; 60% were current or former smokers.
- Histology included 57% patients with non-squamous cell carcinoma and 43% with squamous cell carcinoma.

Table 1. Clinical characteristics of all patients

Clinical Characteristics	Pemb + Plin + Doc (N=30); n (%)
Previously received anti-tumour immunotherapy	
Yes	100%
Age	
Median age, years	68.0 (50–77)
Gender	
Female	26.7%
Male	73.3%
Smoking status	
Non-smoker	40%
Smoker	60%
Histology	
Squamous	43%
Non-squamous	57%

Table 2. Efficacy endpoints

	ITT (N=30)
Primary endpoint	
Confirmed ORR (RECIST 1.1)	21.1%
Secondary endpoints	
Median PFS (RECIST 1.1)	**8.6 months**
Median OS	Not reached
Median DoR (RECIST 1.1)	11.4 months
DCR (PR + SD >4 months)	**89.3% (25/28; 2 patients withdrawn after first dose)**

DCR, disease control rate; DoR, duration of response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; SD, stable disease.

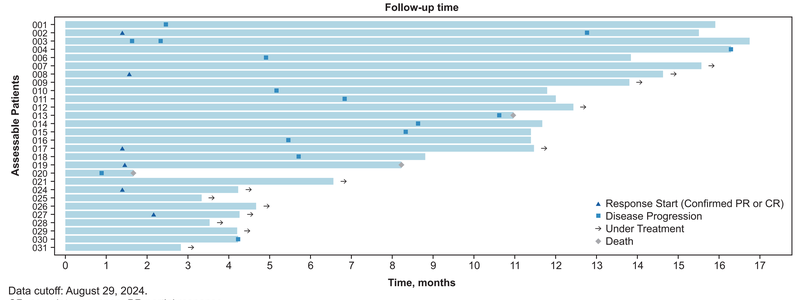
Table 3. Treatment-related adverse events (CTCAE ≥ Grade 3)

System organ class, Preferred term	Pemb + Plin + Doc (N=30), n (%)
All TRAE, CTCAE ≥ Grade 3	14 (46.7)
Blood and lymphatic system disorders	5 (16.7)
Myelosuppression	4 (13.3)
Febrile neutropenia	1 (3.3)
Gastrointestinal disorders	4 (13.3)
Ileus	2 (6.7)
Diarrhea	1 (3.3)
Abdominal distension	1 (3.3)
Investigations	2 (6.7)
Neutrophil count decreased	2 (6.7)
Metabolism and nutrition disorders	1 (3.3)
Hyperglycaemia	1 (3.3)
Acidosis	1 (3.3)
Infections and infestations	2 (6.7)
Lung infection	1 (3.3)
Sepsis	1 (3.3)
Respiratory, thoracic and mediastinal disorders	1 (3.3)
Respiratory failure	1 (3.3)
Vascular disorders	2 (6.7)
Hypertension	2 (6.7)
Renal and urinary disorders	1 (3.3)
Acute kidney injury	1 (3.3)
Cardiac disorders	1 (3.3)
Atrial fibrillation	1 (3.3)

CTCAE, Common Terminology Criteria for Adverse Events; TRAE, treatment-related adverse event.

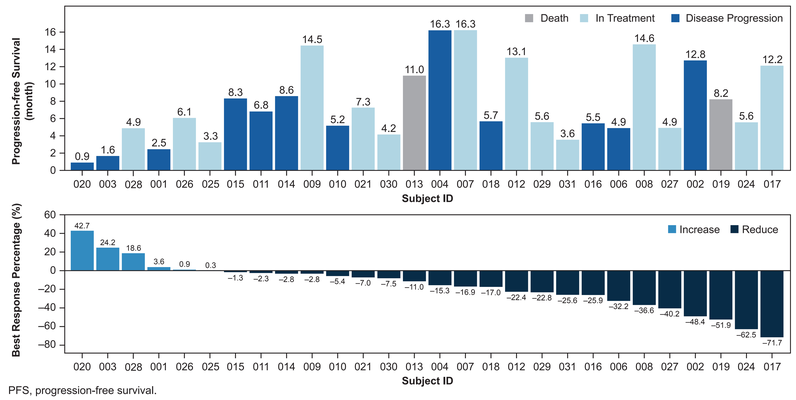
Results

Figure 1. Swimmer plot of tumor response (evaluable patient population)



Data cutoff: August 29, 2024.
CR, complete response; PR partial response.

Figure 2. Waterfall plot of PFS and best response (%) (evaluable patient population)



PFS, progression-free survival.

Conclusions

- Pemb plus Plin and Doc in 30 patients with metastatic NSCLC who experienced disease progression after clinical benefit with ICI had encouraging data with **double PFS (mPFS 8.6 months) and triple DCR (~90% of patients)** compared with historical controls of single agent chemotherapy (mPFS was ~3.7 months with Doc in the TROPION-Lung01 study[6]), with tolerable safety.
- Further investigation into the patients who would benefit from continued ICI treatment after disease progression is warranted. KeyPemls-004 (303 study) is ongoing and further analyses are underway.

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Disclosures

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Use the QR code to find more information about the KeyPemls-004 study protocol