Original Article

# Phase Ib/II study of imprime PGG and pembrolizumab in patients with previously treated advanced non-small cell lung cancer (NSCLC): BTCRC LUN 15-017

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**Background:** Therapeutic strategies to engage anti-tumor innate immunity are still underdeveloped. Imprime PGG (imprime), a pathogen-associated molecular pattern (PAMP), through pattern recognition receptors, successfully illicit a broad-based innate immune response in preclinical models against various cancers. We aimed to study safety and efficacy of imprime in combination with pembrolizumab in advanced stage non-small cell lung cancer (NSCLC).

**Methods:** We conducted an investigator-initiated, multi-institutional, single-arm, phase Ib/II trial in previously treated, advanced stage NSCLC patients. Primary endpoints were maximum-tolerated dose (MTD) of imprime for the phase Ib, and progression-free survival (PFS) for the phase II study (NCT03003468).

**Results:** All 33 eligible patients were included in the safety analysis. No dose-limiting toxicity was observed and the imprime dose of 4 mg/kg was determined as the MTD. Thirty patients treated at the MTD (phase Ib, 6; phase II, 24) were included in the efficacy analysis. Median length of follow-up was 10.8 months. Confirmed objective response rate was 10% [95% confidence interval (CI): 2–27%], with one complete and two partial responses. Median PFS was 2.6 months (95% CI: 1.4–7.0), and 6- and 12-month PFS rates were 37% and 17%, respectively. Median overall survival (OS) was 11.1 months, and 6- and 12-month OS rates were 75% and 46%. Univariate analysis was performed to assess the impact of age, sex, race, disease-stage, programmed death-ligand 1 (PD-L1) expression levels, and prior immunotherapy on PFS and OS. Of these, prior immunotherapy negatively influenced OS [hazard ratio (HR): 2.95, 95% CI: 1.21–7.24]. Overall, the combination was safe and tolerable.

**Conclusions:** The combination of imprime and pembrolizumab is tolerable but did not improve the outcome of advanced stage NSCLC patients who previously progressed on anti-programmed death 1 (PD-1)/PD-L1 immunotherapies. Further investigation is needed to understand the effects of therapeutic PAMPs to mount a strong innate immune response against cancer.

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**Keywords:** Imprime; pathogen-associated molecular pattern (PAMP); innate immunity; non-small cell lung cancer (NSCLC)

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## Introduction

Lung cancer is the second most common cancer and the leading cause of cancer-related mortality in the U.S., accounting for almost 21% of all cancer-related deaths (1). Non-small cell lung cancer (NSCLC) comprises more than 85% of all new cases of lung cancer. Nearly half of these cases have distant disease at diagnosis and exhibit 5-year survival of <10%. Approximately 65% of all NSCLC express some degree of programmed death-ligand 1 (PD-L1) protein on their cell membrane and show a relatively better prognosis with use of anti-programmed death 1 (PD-1)/PD-L1 immunotherapies. However, 35% of advanced stage NSCLC do not express PD-L1. The addition of anti-PD-1/PD-L1 immunotherapies in the treatment paradigm of this NSCLC sub-population has demonstrated only a modest impact on survival (2,3). Nevertheless, many patients who respond to initial anti-PD-1/PD-L1 therapies go on to develop resistance to these agents. Therefore, combinational treatment approaches of various immune-modulating agents may hold a better potential for immune synergy and improve treatment efficacy.

Enhanced trafficking or activation of specific effector T cells in the tumor microenvironment has remained an important strategy in targeting cancers. However, stimulating the innate arm of the immune system is now being increasingly recognized as a complimentary tool to develop effective anti-tumor immunity (4). Both endogenous danger-associated molecular patterns (DAMPs) and exogenous pathogen-associated molecular patterns (PAMPs), are detected by pattern-recognition receptors (PRR) including toll-like receptors (TLRs), nucleotide oligomerization domain (NOD)-like receptors (NLRs), retinoic acid-inducible gene-I (RIG-I)-like receptors (RLRs), C-type lectin receptors (CLRs), and absent in melanoma-2 (AIM2)-like receptors (ALRs) to orchestrate an inflammatory or anti-tumor response through members of the innate arm of the immune system (4-6). Imprime PGG (imprime) is a β-glucan isolated from a proprietary strain of yeast *Saccharomyces cerevisiae* and is safe to administer intravenously. It acts as a PAMP and is sensed by the PRR and orchestrates a robust innate immune response (7,8).

In preclinical models, imprime induced a widespread innate immune response in a Dectin-1-dependent manner (5). It causes production of cytokines, chemokines, and type 1 interferons, activates and enhances natural killer (NK) cell functions, reorients M2 macrophages to an M1 state, facilitates maturation of antigen-presenting dendritic cells, facilitates an anti-tumor T cell-specific response, and synergizes with anti-PD-1 antibody therapy in the murine MC38 tumor model. This makes imprime an attractive combinatorial partner with anti-PD-1/PD-L1 immunotherapies. Clinically imprime has been administered

### Highlight box

**Key findings**

- In this phase Ib/II study, the combination of imprime PGG (imprime) and pembrolizumab was tolerable but did not improve progression-free survival in advanced stage non-small cell lung cancer (NSCLC) patients who previously progressed on anti-programmed death 1 (PD-1)/programmed death-ligand 1 (PD-L1) immunotherapies.

**What is known and what is new?**

- Innate anti-immune response can be complimentary to adaptive immune response. However relatively fewer mechanisms have been explored to investigate the benefits of innate anti-tumor response. Imprime acts as a pathogen-associated molecular pattern and is sensed by the pattern recognition receptors. It can orchestrate a robust innate immune response.
- We explored the safety and effectiveness of the combination of imprime with an anti-PD-1 antibody (pembrolizumab) in advanced stage NSCLC. Imprime and pembrolizumab combination is safe. However, this combination did not improve NSCLC outcomes in patients who are previously progressed on immune checkpoint inhibitors.

**What is the implication and what should change now?**

- Perhaps imprime or therapies stimulating the anti-tumor innate immunity need to be evaluated for synergism either in treatment naïve setting or in biomarker selected patient population in combination with other immunotherapies targeting the adaptive immune system.

at 4 mg/kg weekly with cetuximab, carboplatin, and paclitaxel in patients with advanced stage NSCLC and found to be tolerable (8).

We present an investigator-initiated, multi-institutional, single-arm, phase Ib/II trial evaluating the combination of pembrolizumab and imprime in advanced stage NSCLC. We present this article in accordance with the TREND reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-346/rc).

## Methods

### *Study design*

Big Ten Cancer Research Consortium (BTCRC) LUN 15-017 was a multicenter, investigator-initiated, single-arm, phase Ib–II trial. Three academic medical centers, University of Illinois, Chicago, University of Iowa, and Rutgers Cancer Institute of New Jersey (RCINJ), as part of the BTCRC, participated in the trial.

Eligible patients were 18 years or older, progressed through platinum-based chemotherapy for an advanced stage, pathologically confirmed NSCLC, and naïve to anti-PD-1/PD-L1 therapies (later amended to allow receipt of prior immunotherapy; see Statistical considerations and analyses). Adequate hepatic, renal, and marrow functions were required. Patients had to have Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 and a life expectancy of at least 6 months from the time of registration. Patients with *EGFR* exon 19 del or L858R or *ALK* fusion who progressed through approved tyrosine kinase inhibitors (TKIs) were eligible. Patients enrolled in phase II were required to have measurable disease per RECISTv1.1. Participants with active central nervous system (CNS) metastases, history of solid organ or stem cell transplant, active autoimmune diseases requiring systemic immunosuppression, interstitial lung disease and active hepatitis B or C, human immunodeficiency virus (HIV), or tuberculosis infections were excluded.

### *Study treatment plan*

Dose escalation during phase Ib was planned according to 3+3 design. The initial dose for imprime with pembrolizumab was 2 mg/kg on days 1, 8 and 15 of every 21-day cycle for 4 cycles and then on day 1 of cycles 5 through 16. Three to six patients were to be initially enrolled at 2 mg/kg (dose level 1). If none of the first three patients experienced a dose-limiting toxicity (DLT) during the first cycle, then an additional three patients were to be enrolled at dose level 2 (4 mg/kg). If at most 1 of 3 patients in dose level 2 complete the first cycle of therapy without DLT, then three additional patients were to be enrolled to ensure at most one of six patients had a DLT. No further dose escalation was planned and if tolerable, this dose was considered as the maximum-tolerated dose (MTD). Treatment was continued for up to 16 cycles, until progression, significant toxicity, or withdrawal, whichever occurred first. Patients were monitored for progression every 2 cycles.

### *Statistical considerations and analyses*

The primary objective of phase Ib was to establish the MTD of imprime in combination with pembrolizumab. The primary objective of phase II was to evaluate preliminary evidence of anti-tumor activity of imprime in combination with pembrolizumab by testing the null hypothesis that the median progression-free survival (PFS) is less than a historic estimate of 3.2 months in the immunotherapy naïve patient population in the second-line setting (9,10) versus the alternative that it is 6.3 months or greater. The trial was originally designed to have 90% power to detect a 3.1-month increase in median PFS with two-sided statistical testing performed at the 5% level with a sample size of 24 patients. With the Food and Drug Administration (FDA) approval of anti-PD-1/PD-L1 immunotherapy in the frontline setting for advanced stage NSCLC, inclusion criteria for the trial were modified between phases Ib and II to include patients who had received prior anti-PD-1/PD-L1 immunotherapy with platinum-based chemotherapy or as monotherapy. Thus, comparisons to the historic estimate are no longer considered clinically relevant, and formal statistical testing of the phase II primary endpoint was not performed.

The incidence of treatment-emergent adverse events was summarized by type of adverse event, grade, and attribution, with the most severe grade per patient being reported. The objective response rate was defined as the proportion of patients with a confirmed complete response (CR) or partial response (PR) per RECIST v1.1. The clinical benefit rate was defined as the proportion of patients with a CR, PR, or stable disease (SD). PFS was defined as the time from treatment initiation to the date of first documentation of disease progression or death due to any cause. Otherwise, patients were censored at date of last

 

radiographic assessment. Overall survival (OS) was defined as the time from treatment initiation to death due to any cause. Patients still alive were censored at the last date known to be alive. Survival probabilities were estimated and plotted using the Kaplan-Meier method. Estimates along with 95% pointwise confidence intervals (CIs) are reported. Cox regression models were utilized to estimate the effect of baseline characteristics on PFS and OS. Estimated covariate effects are reported as hazard ratios (HRs) along with 95% CI. All tests were two-sided and assessed for significance at the 5% level using SAS v9.4 (SAS Institute, Cary, NC, USA).

### *Study oversight*

The protocol was submitted to the U.S. FDA under Investigational New Drug 131052 and registered to ClinicalTrials.gov prior to enrollment of the first patient (NCT03003468) (supplementary file 1 available at https://cdn.amegroups.cn/static/public/tlcr-24-346-1.pdf). Participating sites include University of Illinois Chicago Cancer Center (UICCC), Holder Comprehensive Cancer Center (HCCC) University of Iowa and RCINJ. Each participating center's institutional review board approved the study prior to enrolling patients (UIC IRB # 2016-1085, University of Iowa Hawk IRB # 201703873, Rutgers eIRB Pro20170000733) (supplementary file 2 available at https://cdn.amegroups.cn/static/public/tlcr-24-346-2.pdf). Informed written consent was obtained from each patient before participating in the study. The trial was conducted according to the Belmont Report, the United States Common Rule (45CFR§46), and the International Council on Harmonisation-Good Clinical Practice (GCP) as adopted by U.S. federal law. All investigators were GCP trained. The University of Illinois, Chicago Cancer Center's Data and Safety Monitoring Committee (DSMC) reviewed all data for compliance to protocol and participant safety. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Safety and annual reports regarding this trial were submitted as required (21CFR§312.23, §312.32).

## Results

Between Feb 2017 to Sep 2020, a total of 35 patients were registered; 1 patient withdrew consent prior to initiating treatment, and 1 patient was deemed ineligible (no measurable lesions) after initiating treatment. The remaining 33 patients were included in the reported safety analysis. Participant demographics and baseline disease characteristics are described in *Table 1*. No DLT was observed in the phase Ib cohorts at both 2 and 4 mg/kg dose with pembrolizumab. The imprime dose of 4 mg/kg was determined as the MTD. Thirty of 33 patients received imprime at the MTD (phase Ib, 6; phase II, 24) and were included in the efficacy analysis. At the time of data cutoff, the median length of follow-up was 10.8 months (range, 0.0 to 52.8 months). Of the efficacy population, 21 patients were deceased, while 5 patients were alive and had not progressed at the time of data cutoff (*Figure 1*).

Reasons for coming off treatment were as follows: disease progression (n=18), adverse events (n=5), completed protocol defined treatment (n=4), death (n=1), withdrew consent (n=1), reason unspecified (n=1). In the efficacy analysis, the confirmed objective response rate was 10% (95% CI: 2–27%), with one CR and two PRs. The clinical benefit rate was 47% (95% CI: 23–67%). Thirteen patients (43.3%) developed PD as their best overall response, while three patients (10%) were not evaluable for response. *Figures 2A*,*2B* demonstrate patients' disease course and correlates their responses with disease-related factors and outcomes.

In the safety population (n=33), a total of 10 patients experienced serious adverse events (SAE). Three (10%) SAEs were treatment related. Adverse events related to imprime are summarized in *Table 2* and treatment-emergent adverse event occurring with frequency of ≥5% are reported in *Table 3*.

Median PFS was 2.6 months (95% CI: 1.4–7.0), and 6-month and 12-month PFS rates were 37% (95% CI: 20–55%) and 17% (95% CI: 5–34%), respectively (*Figure 3A*). Median OS of 11.1 months was observed, and 6-month and 12-month OS rates were 75% (95% CI: 55–87%) and 46% (95% CI: 28–63%), respectively (*Figure 3B*). We assessed the influence of factors including age, sex, race, disease-stage, level of PD-L1 expression and receipt of prior anti-PD-1/PD-L1 immunotherapy on PFS and OS. Of these, receipt of prior immunotherapy negatively influenced the outcomes (*Figure 3C*,*3D*) and was statistically significant for OS. Univariate analysis for PFS and OS are shown in *Table 4*.

## Discussion

This study was initially designed to explore the safety and the efficacy of the combination of imprime and pembrolizumab in advanced stage NSCLC in the second line setting after progression on platinum-based

 

**Table 1** Patient demographics and disease baseline characteristics

| Covariate | Cohorts | |
|---|---|---|
| | Safety (N=33) | Efficacy (N=30) |
| Age (years) | 66 [53–82] | 66 [53–82] |
| Sex | | |
| Female | 16 (48.5) | 14 (46.7) |
| Male | 17 (51.5) | 16 (53.3) |
| Race | | |
| White | 22 (71.0) | 21 (72.4) |
| Black | 7 (22.6) | 6 (20.7) |
| Asian | 2 (6.5) | 2 (6.9) |
| Missing | 2 | 1 |
| Ethnicity | | |
| Hispanic or Latino | 2 (6.3) | 2 (6.7) |
| Non-Hispanic | 30 (93.8) | 28 (93.3) |
| Missing | 1 | 0 |
| Smoking status | | |
| Never | 5 (15.2) | 5 (16.7) |
| Current | 7 (21.2) | 6 (20.0) |
| Former | 21 (63.6) | 19 (63.3) |
| ECOG score | | |
| 0 | 3 (9.1) | 3 (10.0) |
| 1 | 29 (87.9) | 26 (86.7) |
| 2 | 1 (3.0) | 1 (3.3) |
| Prior platinum therapy | | |
| No | 3 (9.1) | 3 (10.0) |
| Yes | 30 (90.9) | 27 (90.0) |
| Prior immunotherapy | | |
| No | 19 (57.6) | 16 (53.3) |
| Yes | 14 (42.4) | 14 (46.7) |
| T stage | | |
| x–2 | 16 (48.5) | 14 (46.7) |
| 3–4 | 17 (51.5) | 16 (53.3) |
| N stage | | |
| x–1 | 13 (39.4) | 12 (40.0) |
| 2–3 | 20 (60.6) | 18 (60.0) |
| M stage | | |
| 0 | 3 (9.1) | 3 (10.0) |
| 1 | 30 (90.9) | 27 (90.0) |
| Histology | | |
| Non-squamous | 27 (81.8) | 25 (83.3) |
| Squamous | 6 (18.2) | 5 (16.7) |
| PD-L1 | | |
| <1% | 12 (41.4) | 10 (37.0) |
| 1–49% | 12 (41.4) | 12 (44.4) |
| 50–100% | 5 (17.2) | 5 (18.5) |
| Missing | 4 | 3 |

Data are presented as median [range] or n (%). ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed death-ligand 1.

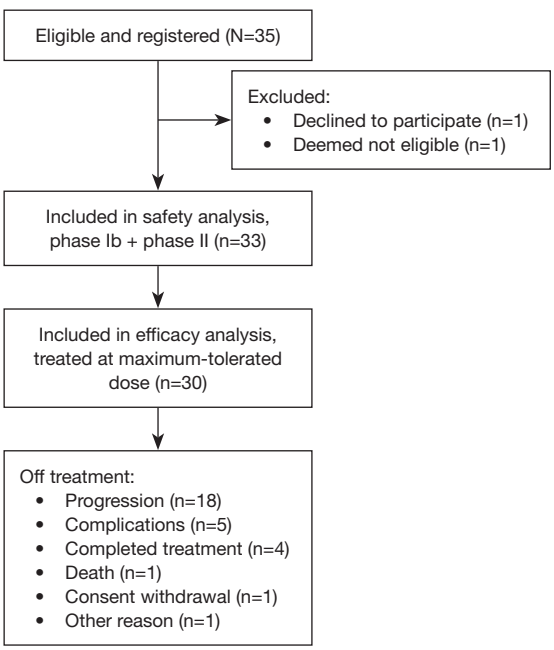


**Figure 1** Flow of participant through the trial.

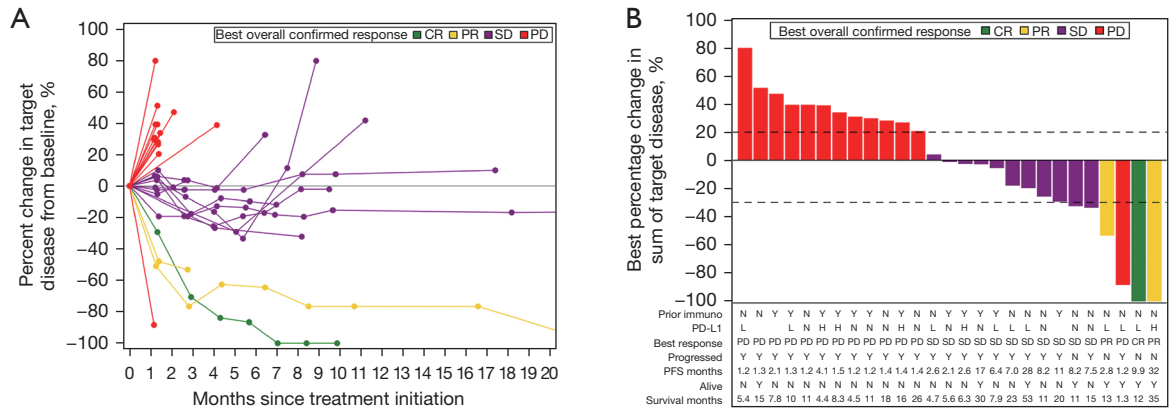


**Figure 2** Changes in target disease per RECIST v1.1. (A) Spider plot; (B) waterfall plot along with disease characteristics and patient outcomes. CR, complete response; PR, partial response; SD, stable disease; PD, disease progression; Immuno, immunotherapy; PD-L1, program death ligand-1; PFS, progression-free survival; N, no or negative; Y, yes; L, low; H, high.

**Table 2** All treatment-related toxicities, maximum grade per patient

| Toxicity | Grade | | | Total |
|---|---|---|---|---|
| | 1 | 2 | 3 | |
| Any toxicity | 7 (21.2) | 15 (45.5) | 5 (15.2) | 27 (81.8) |
| Infusion-related reaction | 1 (3.0) | 10 (30.3) | 2 (6.1) | 13 (39.4) |
| Fatigue/malaise | 9 (27.3) | 1 (3.0) | 0 | 10 (30.3) |
| Nausea/vomiting | 6 (18.2) | 1 (3.0) | 0 | 7 (21.2) |
| Arthralgia/myalgia | 4 (12.1) | 2 (6.1) | 1 (3.0) | 7 (21.2) |
| Pain | 5 (15.2) | 0 | 0 | 5 (15.2) |
| Rash | 4 (12.1) | 0 | 0 | 4 (12.1) |
| Diarrhea | 2 (6.1) | 1 (3.0) | 0 | 3 (9.1) |
| Chills | 1 (3.0) | 2 (6.1) | 0 | 3 (9.1) |
| Dyspnea | 1 (3.0) | 1 (3.0) | 1 (3.0) | 3 (9.1) |
| Anorexia | 2 (6.1) | 0 | 0 | 2 (6.1) |
| Cough | 2 (6.1) | 0 | 0 | 2 (6.1) |
| Flu-like symptoms | 2 (6.1) | 0 | 0 | 2 (6.1) |
| Hypo/hyperthyroidism | 1 (3.0) | 1 (3.0) | 0 | 2 (6.1) |
| Pruritus | 1 (3.0) | 1 (3.0) | 0 | 2 (6.1) |
| Headache | 0 | 2 (6.1) | 0 | 2 (6.1) |
| Anemia | 1 (3.0) | 0 | 0 | 1 (3.0) |
| Bloating/dyspepsia/ flatulence | 1 (3.0) | 0 | 0 | 1 (3.0) |
| Blurred vision | 1 (3.0) | 0 | 0 | 1 (3.0) |
| Dysphagia | 1 (3.0) | 0 | 0 | 1 (3.0) |
| Fever | 1 (3.0) | 0 | 0 | 1 (3.0) |
| Flushing | 1 (3.0) | 0 | 0 | 1 (3.0) |
| Hyperglycemia | 1 (3.0) | 0 | 0 | 1 (3.0) |
| Involuntary movements | 1 (3.0) | 0 | 0 | 1 (3.0) |
| Sinus tachycardia | 1 (3.0) | 0 | 0 | 1 (3.0) |
| Allergic/injection site reaction | 0 | 1 (3.0) | 0 | 1 (3.0) |
| Colitis | 0 | 0 | 1 (3.0) | 1 (3.0) |
| Creatinine increased | 0 | 1 (3.0) | 0 | 1 (3.0) |
| Dizziness | 0 | 1 (3.0) | 0 | 1 (3.0) |
| Hypotension | 0 | 1 (3.0) | 0 | 1 (3.0) |
| Pneumonitis | 0 | 1 (3.0) | 0 | 1 (3.0) |

No grades 4 or 5 treatment-related toxicities were reported. Data are presented as n (%).

chemotherapy. However, shortly after the completion of phase Ib, anti-PD-1/PD-L1 agents received FDA approval and were moved to the first-line setting in advanced stage NSCLC after demonstrating a survival benefit both as monotherapy and in combination with platinum-based chemotherapy (11-15). The study protocol was amended to allow the receipt of anti-PD-1/PD-L1 prior to enrolling in the study. This development after initiation of the trial

**Table 3** Treatment-emergent adverse events occurring with a total frequency of ≥5%

| Toxicity | Grade | | | | | Total |
|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | |
| Any toxicity | 4 (12.1) | 16 (48.5) | 10 (30.3) | 1 (3.0) | 1 (3.0) | 32 (97.0) |
| Pain | 9 (27.3) | 8 (24.2) | 0 | 0 | 0 | 17 (51.5) |
| Infusion-related reaction | 1 (3.0) | 10 (30.3) | 2 (6.1) | 0 | 0 | 13 (39.4) |
| Fatigue/malaise | 10 (30.3) | 2 (6.1) | 0 | 0 | 0 | 12 (36.4) |
| Arthralgia/myalgia | 7 (21.2) | 2 (6.1) | 1 (3.0) | 0 | 0 | 10 (30.3) |
| Nausea/vomiting | 8 (24.2) | 1 (3.0) | 1 (3.0) | 0 | 0 | 10 (30.3) |
| Infection | 1 (3.0) | 7 (21.2) | 0 | 0 | 1 (3.0) | 9 (27.3) |
| Rash | 7 (21.2) | 2 (6.1) | 0 | 0 | 0 | 9 (27.3) |
| Diarrhea | 5 (15.2) | 1 (3.0) | 2 (6.1) | 0 | 0 | 8 (24.2) |
| Anorexia | 6 (18.2) | 1 (3.0) | 0 | 0 | 0 | 7 (21.2) |
| Cough | 5 (15.2) | 1 (3.0) | 0 | 0 | 0 | 6 (18.2) |
| Anemia | 4 (12.1) | 1 (3.0) | 0 | 0 | 0 | 5 (15.2) |
| Dyspnea | 1 (3.0) | 2 (6.1) | 2 (6.1) | 1(3.0) | 0 | 5 (15.2) |
| Headache | 3 (9.1) | 2 (6.1) | 0 | 0 | 0 | 5 (15.2) |
| Bloating/dyspepsia/flatulence | 3 (9.1) | 1 (3.0) | 0 | 0 | 0 | 4 (12.1) |
| Constipation | 3 (9.1) | 1 (3.0) | 0 | 0 | 0 | 4 (12.1) |
| Edema, limbs | 4 (12.1) | 0 | 0 | 0 | 0 | 4 (12.1) |
| Lymphocyte count decreased | 1 (3.0) | 3 (9.1) | 0 | 0 | 0 | 4 (12.1) |
| Pruritus | 1 (3.0) | 3 (9.1) | 0 | 0 | 0 | 4 (12.1) |
| Allergic/injection site reaction | 2 (6.1) | 1 (3.0) | 0 | 0 | 0 | 3 (9.1) |
| Chills | 1 (3.0) | 2 (6.1) | 0 | 0 | 0 | 3 (9.1) |
| Dizziness | 2 (6.1) | 1 (3.0) | 0 | 0 | 0 | 3 (9.1) |
| Hyperglycemia | 3 (9.1) | 0 | 0 | 0 | 0 | 3 (9.1) |
| Hypo/hyperthyroidism | 1 (3.0) | 2 (6.1) | 0 | 0 | 0 | 3 (9.1) |
| Anxiety | 0 | 2 (6.1) | 0 | 0 | 0 | 2 (6.1) |
| Creatinine increased | 0 | 2 (6.1) | 0 | 0 | 0 | 2 (6.1) |
| Depression | 1 (3.0) | 1 (3.0) | 0 | 0 | 0 | 2 (6.1) |
| Fever | 2 (6.1) | 0 | 0 | 0 | 0 | 2 (6.1) |
| Flu-like symptoms | 2 (6.1) | 0 | 0 | 0 | 0 | 2 (6.1) |
| Hemoptysis | 1 (3.0) | 1 (3.0) | 0 | 0 | 0 | 2 (6.1) |
| Insomnia | 2 (6.1) | 0 | 0 | 0 | 0 | 2 (6.1) |
| Nasal congestion | 1 (3.0) | 1 (3.0) | 0 | 0 | 0 | 2 (6.1) |
| Neutrophil count decreased | 1 (3.0) | 0 | 1 (3.0) | 0 | 0 | 2 (6.1) |
| Platelet count decreased | 1 (3.0) | 1 (3.0) | 0 | 0 | 0 | 2 (6.1) |
| Pleural effusion | 0 | 1 (3.0) | 1 (3.0) | 0 | 0 | 2 (6.1) |
| Pneumonitis | 1 (3.0) | 1 (3.0) | 0 | 0 | 0 | 2 (6.1) |

Data are presented as n (%).

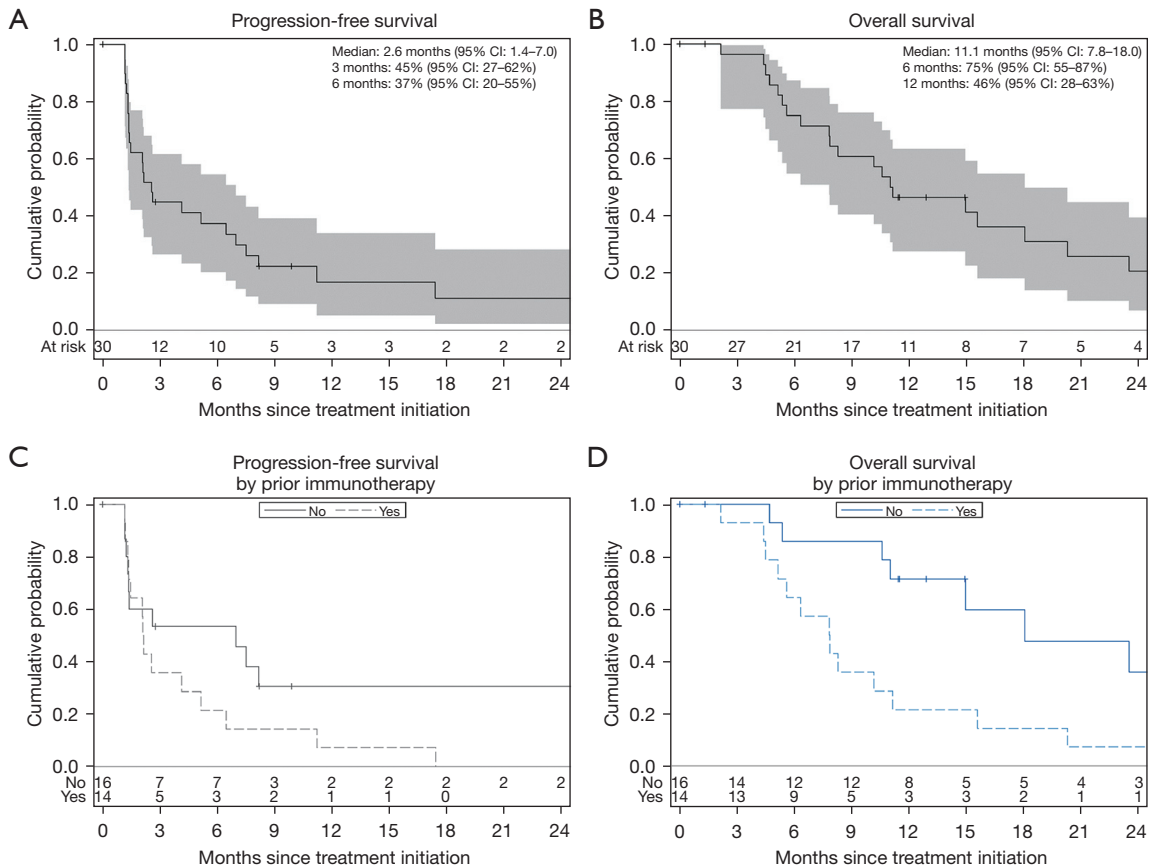


**Figure 3** Kaplan-Meier curves. (A) PFS; (B) OS; (C) PFS by receipt of prior immunotherapy; (D) OS by receipt of prior immunotherapy. CI, confidence interval; PFS, progression-free survival; OS, overall survival.

explains why patients who did not receive anti-PD-1/PD-L1 therapies prior to participating in this study did better. In the overall patient population, median PFS was 2.6 months, which is no better than docetaxel, an FDA approved second-line chemotherapy. However, patients who were immunotherapy naïve, had a relatively longer PFS and OS. In CheckMate 057 and 017 studies, the median PFS of patients who received docetaxel, was 4.2 and 2.8 months respectively while median OS was 9.4 and 6.0 months respectively (9,10).

Improving clinical outcomes for patients with NSCLC after progression on combination of platinum-based chemotherapy and anti-PD-1/PD-L1 immunotherapies continues to remain a major challenge. Nivolumab, atezolizumab and pembrolizumab have been shown to improve 1-year PFS and OS over docetaxel (9,10,16,17). However, since these agents moved to the first-line setting, docetaxel with or without ramucirumab continues as the standard second-line option for these patients. Three different classes of agents are currently under investigation to improve NSCLC outcomes in the second-line setting: (I) drugs invigorating the innate arm of the immune system against NSCLC; (II) agents enhancing the adaptive arm of the immune system; and (III) antibody drug conjugates (ADC).

Several mechanisms to harness anti-tumor innate immunity, such as TLR, STING, and CD40 agonists, indoleamine 2,3-dioxygenase (IDO) inhibitors, inhibitory antibodies to KIR and NKG2A, and adoptive NK cell transfer are being evaluated in clinical trials (18). Similarly, multiple early phase studies have shown encouraging results with anti-TIM3, anti-TIGIT, anti-LAG3, OX-40 agonist, and 41BB agonist (19-24). Drugs employing adaptive immune system checkpoints are further along in clinical development than agents orchestrating the innate arm of the immune system.

**Table 4** Univariate analysis for progression-free and overall survival

| Covariate | N | Progression-free survival | | | Overall survival | | |
|---|---|---|---|---|---|---|---|
| | | Hazard ratio | 95% CI | P value | Hazard ratio | 95% CI | P value |
| Sex | | | | 0.74 | | | 0.35 |
| Male | 16 | 1.15 | (0.51–2.60) | | 1.53 | (0.63–3.69) | |
| Female | 14 | Ref | | | Ref | | |
| Non-Hispanic, White | | | | 0.59 | | | 0.49 |
| No | 10 | 0.78 | (0.32–1.91) | | 0.68 | (0.23–2.04) | |
| Yes | 19 | Ref | | | Ref | | |
| Prior immunotherapy | | | | 0.13 | | | 0.02 |
| Yes | 14 | 1.91 | (0.83–4.36) | | 2.95 | (1.21–7.24) | |
| No | 16 | Ref | | | Ref | | |
| T stage | | | | 0.06 | | | 0.12 |
| 3–4 | 16 | 0.46 | (0.20–1.03) | | 0.50 | (0.21–1.21) | |
| x–2 | 14 | Ref | | | Ref | | |
| N stage | | | | 0.26 | | | 0.27 |
| 2–3 | 18 | 1.66 | (0.69–3.96) | | 1.66 | (0.68–4.04) | |
| x–1 | 12 | Ref | | | Ref | | |
| PD-L1 | | | | 0.57 | | | 0.68 |
| 1–100% | 17 | 0.78 | (0.32–1.87) | | 1.21 | (0.49–3.03) | |
| <1% | 12 | Ref | | | Ref | | |
| Age (units =1 year) | 30 | 1.00 | (0.95–1.06) | 0.93 | 1.00 | (0.94–1.06) | 0.92 |

PD-L1, programmed death-ligand 1; CI, confidence interval; Ref, reference.

While ADC are even further along in development, these drugs are relatively toxic compared to immunotherapies. Datopotamab deruxtecan (Dato-DXd) is a TROP2 ADC. It has recently demonstrated a statistically significant improvement in PFS over docetaxel (25). Other ADCs, such as BL-B01D1 (EGFRxHER3 bispecific ADC), patritumab deruxtecan (HER3-DXd), and tusamitamab ravtansine (anti-CEACM5 ADC), are currently in phase I/II trials and showing promising results in select patient populations (26-28).

There are a few limitations to our study. The study enrollment period was relatively long and the change in the standard of care for first- and second-line therapy for advanced stage NSCLC during the study period affected the study design, accrual, and interpretation of results. In addition, it was a small signal seeking study evaluating the synergistic activity of the combination of pembrolizumab and imprime.

## Conclusions

The combination of imprime and pembrolizumab is tolerable; however, it did not improve advanced stage NSCLC outcomes in patients who were previously treated with anti-PD-1/PD-L1 immunotherapies. Further investigation is needed to determine the effects of therapeutic PAMPs and to discover approaches for harnessing the anti-tumor innate immune system.

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## Footnote

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