A Phase Ib Open-Label, Multicenter Study of Inhaled DV281, a TLR9 Agonist, in Combination with Nivolumab in Patients with Advanced or Metastatic Non–small Cell Lung Cancer

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ABSTRACT

Purpose: Although PD-(L)1 inhibitors have shown efficacy in advanced/metastatic non–small cell lung cancer (NSCLC), many patients do not respond to this treatment and more effective combinations with acceptable toxicities are needed. To assess the potential benefit of combining localized innate immune stimulation with checkpoint blockade, the TLR9 agonist DV281 was combined with nivolumab in a phase Ib study.

Patients and Methods: Patients after one or two prior lines of systemic therapy were enrolled in a dose-escalation study with a 3+3 design. DV281 was administered via inhalation in five dose cohorts at 1 to 25 mg; nivolumab 240 mg was administered intravenously every 2 weeks. Safety, tolerability, pharmacodynamics, and response to treatment were assessed.

Results: Twenty-six patients with advanced NSCLC enrolled. Baseline programmed death ligand 1 (PD-L1) expression was present in 16 patients (61.5%); 21 (80.7%) had received previous anti–PD-1/PD-L1. Thirteen patients (50%) had stable disease, nine (34.6%) had progressive disease, and four (15.4%) were not evaluable. Median duration of disease control was 124 days. Adverse events were seen in 16 patients (61.5%), mostly grade 1/2 chills, fatigue, flu-like symptoms, diarrhea, and rash; there was only one grade 3 adverse event (dyspnea). Pharmacodynamic assessment, measured by IFN- inducible gene expression, showed target engagement in all dose cohorts. Systemic pharmacodynamic responses plateaued in the 2 highest dose cohorts.

Conclusions: DV281 with nivolumab was well tolerated with target engagement observed at every dose. Pharmacodynamic advantages at doses above 10 mg were unclear. The long duration of disease control in 50% of patients suggests clinically relevant activity in this population of heavily pretreated patients.

Introduction

Lung cancer is the leading cause of cancer-related death (1). Non–small cell lung cancer (NSCLC) accounts for 84% of all lung cancer diagnoses (1). In recent years, the treatment of NSCLC has changed dramatically, and immunotherapy alone or in combination with chemotherapy has become the standard first-line treatment for metastatic NSCLC without *EGFR* or *ALK* genetic alterations based on results of phase III trials that demonstrated significant overall survival (OS) benefit (2–5). Patients with programmed death ligand 1 (PD-L1) expression of 1% or greater can receive treatment with pembrolizumab as monotherapy (or atezolizumab monotherapy with high-level expression) or combination nivolumab/ipilimumab (6–8). Regardless of the level of PD-L1 expression, various combinations of immunotherapy plus platinum-based chemotherapy are effective options (3, 4, 9, 10). The rationale for these chemo-immunotherapy combinations is based on two mechanisms: induction of immunogenic cell death and disruption of the immune-suppressive tumor microenvironment (11, 12). Despite this progress, however, OS and PFS rates remain disappointing, and there is still a high unmet need for regimens that confer increased efficacy while minimizing toxicity.

Immune checkpoint inhibitors such as anti–PD-1 and anti–PD-L1 increase the function of tumor-responsive T cells but are much more effective in patients with preexisting immune infiltration, as assessed by PD-L1 expression in tumor biopsies (13). In mouse transplantable tumor models, local activation of dendritic cells by intratumoral injection of a TLR9 agonist induces significant antitumor immunity, which is substantially enhanced by combination with a PD-1 inhibitor (11). The combination of TLR9 activation and PD-1 inhibition acts by increasing both the numbers of tumor-infiltrating T cells as well as the cytotoxic functions of those cells, and it is therefore hypothesized that an effective antitumor immune response would be enhanced by the combination. Localized TLR9 activation paired with PD-1

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Translational Relevance

Checkpoint blockade inhibitors have revolutionized the treatment of non–small cell lung cancer (NSCLC), but only a minority of patients have clinical responses, with only a fraction of these responses being durable. New combinations of well-tolerated approaches are urgently needed. One strategy to enhance antitumor immune response is to activate toll-like receptors (TLRs). TLR agonists can increase the production of inflammatory cytokines and type I IFNs, reinvigorating adaptive immune responses. Toll-like receptor 9 (TLR9), which responds to unmethylated CpG-DNA, has promising preclinical activity and has been of particular clinical interest. Here we present a phase Ib trial of an inhaled TLR9-agonist, DV281, in combination with nivolumab in previously treated patients with NSCLC, the majority of whom had previously received immune checkpoint inhibitors. The tolerability and long duration of disease control in this population suggests clinically relevant activity, and the results can inform future studies assessing efficacy of this approach.

blockade is being studied in injectable human tumors with especially promising responses observed in patients with advanced melanoma (14). In both mouse and human studies, injection of a single tumor lesion appeared sufficient to generate regression in noninjected as well as injected tumor lesions.

For NSCLC, tumor sites easily accessible for repeated injection are uncommon; however, effective localized delivery can be achieved by inhalation of an aerosolized TLR9 agonist solution. In mouse models of tumors with prominent lung metastases, inhaled CpG motifs generated significant T-cell–mediated antitumor activity, and combination with an anti–PD-1 antibody resulted in systemic antitumor T-cell responses that cleared metastatic tumors in the lung as well as in nontreated organs (15).

The TLR9 agonist DV281 is a synthetic oligonucleotide with optimized CpG motifs (CpG-ODN) that mimics the immunostimulatory activity of microbial DNA. DV281 is a C-class CpG-ODN (16) designed to activate both functional maturation and type-I IFN production in TLR9-expressing plasmacytoid dendritic cells, the principal target cell for this therapeutic strategy. In humans, CpG-ODNs with similar structure and activity, such as AZD1419, have been shown to be safe and pharmacologically active when delivered repeatedly by nebulization to healthy volunteers (17) and patients with asthma (18). This phase Ib study combined intravenously delivered nivolumab and DV281 administered via nebulized inhalation with a dose escalation of DV281 to assess safety of the combination and confirm target engagement.

Patients and Methods

Patients

Patients included in the trial were adults 18 years or older with histologically or cytologically confirmed advanced NSCLC and at least one lung lesion measurable per RECIST v1.1. Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0, 1, or 2 and adequate bone marrow, liver, renal, and lung functions were required. Patients must have progressed after a first or second line of systemic therapy and received previous platinum-based chemotherapy or specific targeted therapy if their cancer harbored genomic abnormalities in *EGFR* or *ALK* genes. They could be anti–PD-1/PD-L1 experienced or naïve. Exclusions included symptomatic brain metastases, severe underlying pulmonary disease (inclusive of history of pneumonitis, chronic obstructive pulmonary disease requiring emergency care or hospitalization within the prior year, and/or pulse oximetry less than 88% on room air), immunodeficiency, autoimmune disease requiring immunosuppression, or active hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) infection. Eligible patients had to be able to use an inhaler and could not be pregnant, breastfeeding, or expecting to conceive or father children within the projected duration of the trial through 150 days after the last dose of study treatment.

Study objectives and design

This trial was a phase Ib, dose-escalation study with increasing doses of DV281 in combination with a fixed dose of nivolumab in a modified 3+3 design (**Fig. 1**). Beginning with cohort 2, an intrapatient dose escalation of DV281 was performed between doses 1 and 2 (days 1 and 8) and preceded the introduction of nivolumab on day 15. The doses of DV281 tested as monotherapy were 1 mg in cohort 1 (no intrapatient escalation); 1 and 3 mg in cohort 2; 3 and 10 mg in cohort 3; 10 mg and 15 mg in cohort 4; and 15 and 25 mg in cohort 5. The higher dose for each cohort was then continued in combination with nivolumab. DV281 was administered by Vectura's Akita Jet breath-actuated inhaler (Chippenham, United Kingdom) at weekly intervals for eight doses, discontinued for 5 weeks, and restarted with an every-2-week frequency for a total of 21 doses. The total inhaled volume for each dose was 1.5 mL regardless of dose level. The number of breaths needed to administer the full dose could vary by subject depending on the comfort and lung capacity of the subject and was guided by the machine. Patients were observed throughout the inhalation period and for 30 minutes after completion. Nivolumab was given i.v. at 240 mg every 2 weeks starting at week 3. Patients were observed for dose-limiting toxicities (DLTs) for 28 days after starting DV281. Treatment was terminated for DLT or otherwise unacceptable toxicity, investigator or patient decision, or progressive disease (PD) by RECIST v1.1 (19). Patients with asymptomatic PD felt to be benefiting from treatment by the investigator were allowed to continue if they signed an informed consent form for treatment beyond radiographic progression.

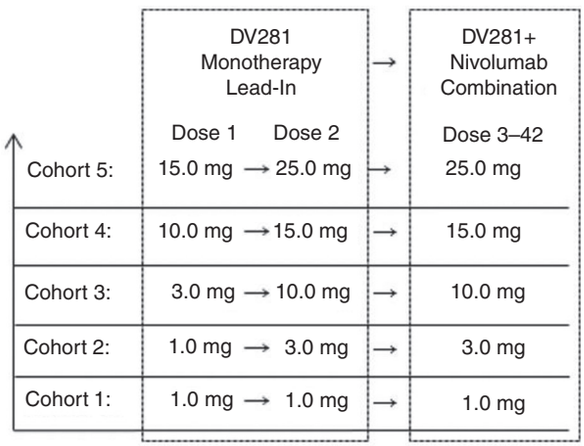


Figure 1.
3+3 design with staggered dosing and intrasubject dose escalation.

The primary endpoints for the study were the safety and tolerability of DV281 as monotherapy and in combination with nivolumab and the identification of a preliminary recommended phase II dose (RP2D). Secondary endpoints included demonstration of target engagement and preliminary efficacy of DV281 in combination with nivolumab. The exploratory endpoints were the relationship between antitumor activity and the biomarkers suggested by the pharmacodynamic assessment of IFN. The study was approved by institutional review boards (IRBs) at each participating center. The study was conducted according to the Declaration of Helsinki and Good Clinical Practices. Written informed consent was obtained prior to enrollment.

Outcome measures

Safety

The safety of DV281 as monotherapy and in combination with nivolumab was assessed based on adverse events (AEs) reporting, vital signs, physical examination, electrocardiograms, and laboratory tests. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf). DLTs were defined as AEs occurring in the 28 days following the first dose of DV281 considered potentially related to DV281 and/or nivolumab that fulfilled at least one of the following criteria: grade ≥3 nonlaboratory AEs, including flu-like symptoms and any respiratory problems associated with grade 3 or higher hypoxia; nausea, vomiting, or diarrhea lasting more than 3 days despite interventions; clinically significant grade 3 and all grade 4 nonhematological laboratory abnormalities; grade ≥3 thrombocytopenia with bleeding or neutropenia with fever; grade 4 anemia or neutropenia lasting more than 7 days.

Pharmacodynamic evaluation of TLR9 activation

Whole blood samples were collected in PAXgene tubes prior to dosing and approximately 24 hours after dosing at the first three administrations of DV281. Predose samples were collected on days 1, 8, and 15, and postdose samples were collected on days 2, 9, and 16. RNA was isolated from blood using the Qiagen PAXgene Blood RNA Kit according to the manufacturer's recommended protocol and analyzed at Core Diagnostics (Hayward, CA) with the nCounter PanCancer Immune Profiling Panel by NanoString Technologies, Inc. (Seattle, WA). Nanostring data were analyzed using the nSolver Analysis Software. A composite score for each sample was generated by calculating the geometric mean of the expression level of a type I IFN signature consisting of 15 genes previously known to be induced by type-1 IFNs: *BST2, CCL2, CXCL10, IFI35, IFIT1, IFIT2, IFITM1, IRF7, ISG15, ISG20, LAMP3, MX1, OAS3, STAT1*, and *STAT2*. An arithmetic mean of postdose samples at each dose level was used establish the relationship between the DV281 dose and the IFN signature response.

Efficacy

Preliminary efficacy was assessed by objective response rate (ORR), duration of response (DOR), disease control rate (DCR), progression-free survival (PFS), and overall survival (OS). Assessments of response and progression for determining study efficacy endpoints were based on response evaluation criteria in solid tumors version 1.1 (RECIST v 1.1; ref. 19). Management of subject on-study treatment and confirmation of PD were based on the immune-related response evaluation criteria in solid tumors (irRECIST) modification of RECIST v 1.1 (20, 21). Disease evaluation was performed at week 10 and then every 9 weeks. For the calculation of PFS, an initial PD per RECIST v1.1 required confirmation with a follow-up scan obtained at least 4 weeks later per irRECIST (22). Median PFS and OS were estimated using the Kaplan–Meier method and compared between groups using nonparametric log-rank tests. The patients were followed for survival until the end of study.

If a confirmed PD occurred during the DV281 only treatment period, the patient's participation was discontinued. At any time during the study, if nivolumab was discontinued, then DV281 also had to be discontinued. Subjects who discontinued both DV281 and anti–PD-1 inhibitor were followed for assessment of response and progression until confirmed PD and then followed for survival. However, the patient could be allowed to continue if the subject was clinically stable per the investigator and sponsor medical monitor, if the safety profile was acceptable, and if the patient was willing and able to continue treatment.

Results

Patients

Twenty-six patients were enrolled in the study from October 5, 2017 to April 15, 2019. Baseline characteristics of the patients are displayed in **Table 1**. Nineteen patients had adenocarcinoma and seven had squamous cell carcinoma (SCC). Nineteen patients had stage IV disease, four had stage IIIA disease, and three had stage IIIB disease. Twelve of the patients had a measurable lesion outside of the lung. Twenty-five (96.2%) patients had received a previous systemic treatment including 14 (53.8%) patients who had received one line of systemic therapy and 11 (42.3%) who had received two lines. Twenty-one patients (80.7%) had previously progressed on a PD-1/PD-L1 inhibitor, either as single agent ($n = 4$, 15.4%) or in combination with chemotherapy ($n = 17$, 65.4%; Supplementary Table S1). The best response with any previous treatment had been partial response (PR) in six patients (23.1%), stable disease (SD) in 13 (50.0%), PD in five patients (19.2%), and could not be assessed in two (7.7%).

Safety

Safety events were recorded for all patients for the duration of the study and are summarized in **Table 2**. In general, adverse events were mild and brief in duration. There was only one significant treatment-related AE, which was a grade 3 treatment-related dyspnea which occurred 9 hours after the third dose of inhaled 25 mg of DV281 and intravenous nivolumab. Oxygen saturation was 93%, and the dyspnea improved with oxygen by nasal cannula and quickly resolved without a requirement for further supplemental oxygen.

The most frequent treatment-related AEs were pruritis, chills, fatigue, and rash. There was no increase in the frequency or severity of reported AEs at higher DV281 dose levels. There additionally were no immune-related AEs, even in the population of patients naïve to PD-1 inhibition. At the time of analysis, 25 patients had discontinued treatment: 15 due to PD, four due to an AE, two per physician decision after continuing beyond PD, and four for other reasons/withdrawal of consent. In all of the patients with AEs leading to treatment discontinuation, the relevant AE(s) were unrelated to study treatment: (i) grade 4 hypercalcemia, (ii) grade 3 atrial flutter and grade 3 pulmonary embolism, (iii) grade 3 syncope, and (iv) grade 1 fatigue.

Pharmacodynamics of DV281

On average, subjects took approximately 124 breaths (range, 29–594) to inhale the full dose of DV281. Circulating blood levels

Table 1. Patient demographic and disease characteristics at baseline.

Characteristics	Cohort 1 (*N* = 4)	Cohort 2 (*N* = 3)	Cohort 3 (*N* = 7)	Cohort 4 (*N* = 7)	Cohort 5 (*N* = 5)	Total (*N* = 26)
Median age, years (range)	64.0 (27–70)	67.0 (59–67)	68.0 (44–85)	56.0 (49–78)	72.0 (53–77)	67.0 (27–85)
Age group						
<65 years	2 (50.0)	1 (33.0)	3 (42.9)	4 (57.1)	1 (20.0)	11 (42.3)
>65 years	2 (50.0)	2 (66.0)	4 (57.1)	3 (42.9)	3 (80.0)	15 (57.7)
Male, *n* (%)	1 (25.0)	1 (33.3)	4 (57.1)	5 (71.4)	1 (20.0)	12 (46.2)
ECOG PS, *n* (%)						
0	0	2 (66.7)	4 (57.1)	0	1 (20.0)	7 (26.9)
1	4 (100)	1 (33.3)	3 (42.9)	7 (100)	4 (80.0)	19 (73.1)
Histology:						
Squamous	2 (50.0)	1 (33.3)	1 (14.3)	2 (28.6)	1 (20.0)	7 (26.9)
Nonsquamous	2 (50.0)	2 (66.7)	6 (85.7)	5 (71.4)	4 (80.0)	19 (73.1)
Stage[a] at screening, *n* (%)						
IIIA	0	0	2 (28.6)	2 (28.6)	0	4 (15.4)
IIIB	1 (25.0)	0	1 (14.3)	1 (14.3)	0	3 (11.5)
IV	3 (75.0)	3 (100)	4 (57.1)	4 (57.1)	5 (100)	19 (73.1)
PD-L1 expression, *n* (%)						
Positive[b]	3 (75.0)	1 (33.3)	4 (57.1)	4 (57.1)	4 (80.0)	16 (61.5)
Negative	1 (25.0)	2 (66.7)	3 (42.9)	3 (42.9)	1 (20.0)	10 (38.5)
Oncogenic mutations, *n* (%)						
KRAS	0	0	1 (14.3)	1 (14.3)	2 (40.0)	4 (15.4)
EGFR	1 (25.0)	0	0	1 (14.3)	1 (20.0)	2 (7.7)
HER2	0	1 (33.3)	0	0	0	1 (3.8)
ALK	0	0	0	0	0	0
BRAF	0	0	1 (14.3)	0	0	1 (3.8)

Abbreviations: ALK, anaplastic lymphoma kinase rearrangement; BRAF, v-Raf murine sarcoma viral oncogene homolog B; EGFR, epidermal growth factor receptor; KRAS, Kirsten rat sarcoma virus homolog.

[a]Staging performed per American Joint Committee on Cancer version 7.

[b]Positive denoted by tumor proportion score greater than 1%.

of DV281 after inhalation were below levels of quantitation (lower limit of quantitation = 5 ng/mL) for nearly all samples taken in cohorts 4 (15 mg) and 5 (25 mg); consequently, samples from cohorts 1 to 3 were not evaluated. Blood samples were collected from each patient before and 24 hours after each of the first three doses of DV281, and the composite expression scores for a panel of known IFN-regulated genes were compared in pre- and postdose samples. Substantial induction of IFN-regulated genes was observed at all dose levels tested and at all three time points (**Fig. 2A**). This induction, however, was transient, and gene expression levels returned to baseline within 6 days. The mean expression scores describe a clear dose-response relationship with significant activity as low as the 1-mg dose and maximum induction at doses of 10 mg and higher (**Fig. 2B**).

Efficacy

The median duration of follow-up was 9.7 months (range, 5–93 months). Based on an intention-to-treat analysis, 13 patients (50%) had SD, nine (34.6%) had PD, and four (15.4%) were not evaluable (**Fig. 3**). There were no objective responses. The median duration of disease control was 4.1 months (Supplementary Table S2). Median PFS was 2.8 months (95% CI, 2.1–5.7); the PFS rate at 6 months was 25.5%. All progression events were based on either new lesions or progression in nontarget lesions. Median OS was 14.1 months (95% CI, 5.7–not reached); OS rate at 12 months was 57.3%. When results were stratified by baseline tumor PD-L1 expression greater than 1%, nine of 16 (56.3%) PD-L1–positive patients had stable disease compared with four of 10 (40%) PD-L1–negative patients (Supplementary Table S3).

The best percent response was in a patient who presented with stage IV nonsquamous lung carcinoma with lymph node and pleural involvement. This patient was resistant to pembrolizumab with a best prior treatment response of confirmed PD. At

Table 2. AEs considered to be drug-related by investigators.

Treatment-related AE, *n* (%)[a]	Total (*N* = 26 patients)
Any	16 (61.5)
Grade 3–4	1 (3.8)[b]
Chills	5 (19.2)
Myalgia	1 (3.8)
Dyspnea	1 (3.8)[b]
Influenza-like symptoms	2 (7.7)
Pyrexia	2 (7.7)
Fatigue	4 (15.4)
Rash	4 (15.4)
Pruritus	6 (26.1)
Angioedema	1 (3.8)
Vomiting	1 (3.8)
Diarrhea	3 (13.0)
Any immune-related AEs	0
AEs leading to d/c of either or both drugs	4 (15.4)
Serious AEs	1 (3.8)[b]
Death	0

[a]*n* (%) reflects number of patients with each event.

[b]Grade 3 treatment-related dyspnea, same single event reflected as dyspnea AE, grade 3–4 AEs, and serious AEs.

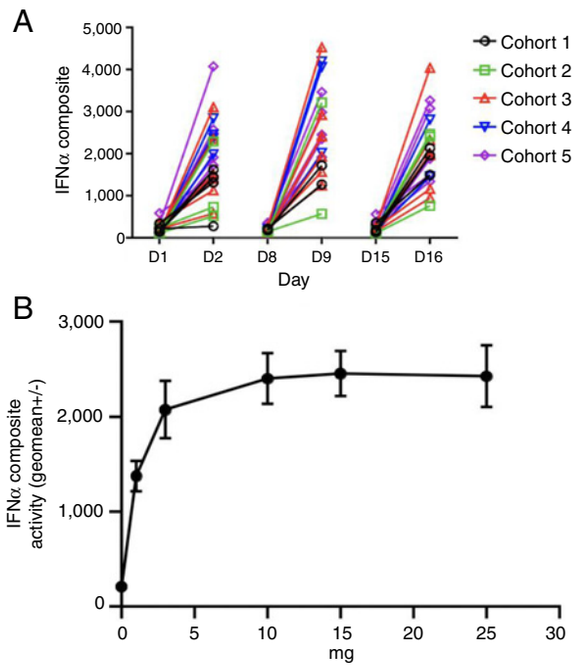


Figure 2.

IFNα correlative studies. **A,** Subjects in all dose cohorts show evidence of target engagement by DV281. Pre- and postdose IFN signature composite scores for each subject prior to (days 2, 8, and 15) and 24 hours after (days 2, 9, and 16) each of the first three administrations of DV281. **B,** IFN signature composite scores demonstrate dose-dependent TLR9 engagement that plateaus at DV281 doses of 10 to 25 mg. Geomean of postdose IFN signature composite activity by dose level, with 95% confidence intervals (CI). The point at a dose of zero is a geomean of all predose samples.

enrollment, she presented with severe dyspnea and bone pain. She was allocated to cohort 5 and received 25 mg of DV281 with nivolumab. By day 50, she experienced dramatic improvement in her symptoms with resolution of her dyspnea and bone pain. Comparison of her baseline and interval CT scan showed a 22% reduction in her target lesions per RECIST v1.1 (**Fig. 4**). She had controlled disease after 7 months of treatment.

Discussion

Local activation of innate immunity by TLR9 agonists is a promising approach to cancer immunotherapy (23), particularly when combined with PD-1/PD-L1 blockade (11, 14). Repeated intratumoral injection is feasible primarily for tumor types with readily accessible lesions, however, for lung tumors, delivery by inhalation presents an alternative. The feasibility of this approach has been validated by studies in mouse metastatic tumor models in which inhalation of a TLR9 agonist led to clearance of metastases in the lung and at extrapulmonary sites (15, 24).

As part of our exploratory analysis, intrapatient dose escalation allowed for a more accurate assessment of the relationship between inhaled DV281 dose and the markers of TLR9 engagement. The low level of systemic bioavailability is consistent with prior studies with a different inhaled CpG-ODN (17) and the broader observation that inhaled ODN are largely retained within the lung (25), supporting the safety of the inhalation route. Nevertheless, based on the increased expression of IFN-regulated genes irrespective of detectable blood levels, it can be assumed the TLR9-dependent induction of type-I IFNs from plasmacytoid dendritic cells provides the basis for a sensitive and robust assessment of the dose-response relationship of inhaled DV281.

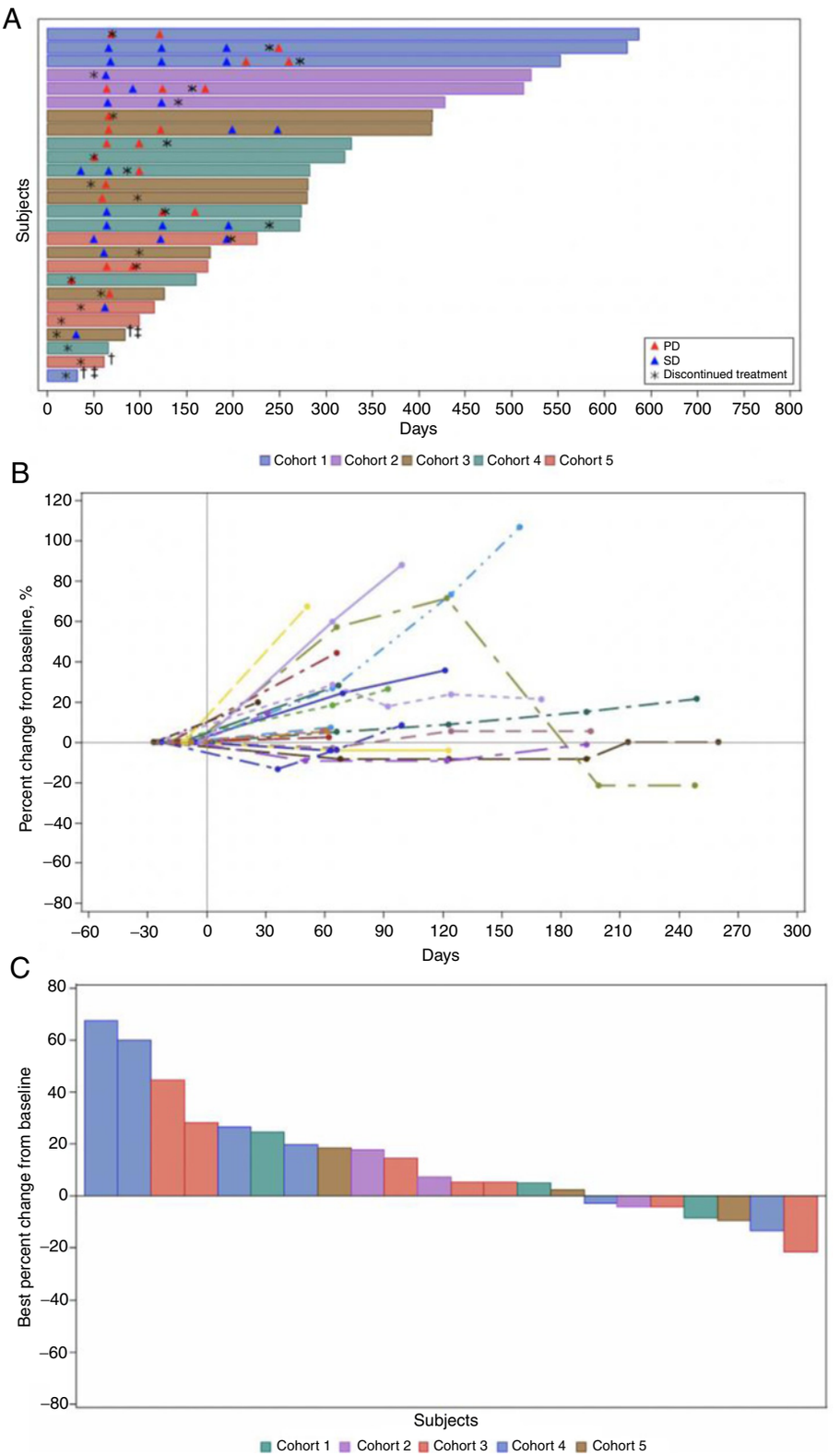
Interestingly, although the safety and tolerability of DV281 was similar across the dose range of 1 mg to 25 mg, pharmacodynamics, as assessed by the induction of IFN-inducible genes in blood leukocytes, described a clear, saturable, dose-response relationship with maximum stimulation reached at doses of 10 mg or more. This response pattern was comparable to that observed in healthy volunteers using a structurally similar inhaled CpG-ODN (17), suggesting that advanced lung cancer patients remained responsive to TLR9 stimulation, despite their significant tumor burden and prior, often cytotoxic, treatment history. Prior studies with TLR9 agonists in patients with cancer have not yet established a correlation between this direct measure of activation and clinical efficacy, and this study is no different. Experience from the SYNERGY-001 study, evaluating the intratumoral CpG-ODN SD-101 in patients with anti–PD-1 treatment-naïve advanced melanoma, suggests that doses suboptimal for TLR9-mediated IFN induction provide greater tumor efficacy than higher doses (26). Based on these considerations, we recommend that two dose levels, 1 mg and 10 mg, be explored in a subsequent expansion study to allow final dose selection to be based firmly on clinical efficacy.

As in any study, there are limitations. First, 26 patients divided across several dose levels limits evaluation of the effects of treatment. In particular, the low number of patients naïve to PD- 1/PD-L1 inhibition, the population most likely to derive benefit, limit ability to contextualize the data. Although effects are expected to be systemic, the fact that standard radiographic analyses don't differentiate intrapulmonary and extrapulmonary lesions along with the lack of a formalized plan per protocol make it challenging to differentiate responses by location. In addition, as some patients with advanced NSCLC do not have a measurable lesion in the lung, our population does not represent all patients with advanced NSCLC.

Ultimately, although optimal second-line treatment after progression on checkpoint inhibitors and/or chemotherapy in PD-L1–positive lung cancer has not yet been established (27, 28), additional options are needed. In a recent retrospective study, Costantini and colleagues reported that the drugs most frequently used after nivolumab were gemcitabine (23%), docetaxel (22%), and erlotinib (16%), with very short median PFS of 2.8, 2.7, and 2.0 months, respectively (27). In this phase Ib escalation study, the combination of DV281 and nivolumab was well tolerated with excellent compliance. The adverse events related to DV281, chills and flu-like symptoms, were generally mild and short-lasting in accordance with previous studies with a different CpG-ODN given intratumorally (14). No objective responses were observed in these heavily pretreated cohorts, but 50% of patients had confirmed disease control with a prolonged duration of disease control of over 4 months with one patient maintaining dramatic clinical improvement for more than 6 months, suggesting clinically relevant activity worthy of further investigation. The approach to development of DV281 in the rapidly evolving field of immunotherapy for NSCLC is being evaluated.

Figure 3.

Subject responses.Time on trial (intention-to-treat population). **A,** Time on trial (intention-to-treat population). Swimmer plot depicting time on trial. Confirmed SD was observed in six patients; five had unconfirmed SD, two exhibited unconfirmed SD after stopping treatment; nine patients had PD; four patients were unevaluable. †Three patients had study treatment withdrawn due to adverse events. ‡Two patients never received nivolumab. **B,** Percent change in tumor size from baseline over time in target lesion(s) (intention-to-treat population). There were no objective responses. **C,** Maximum percent change in sum of the longest diameter from baseline in target lesion(s). Of 22 evaluable patients, best response was SD in 16 patients (72.7%) and PD in six (27.3%).



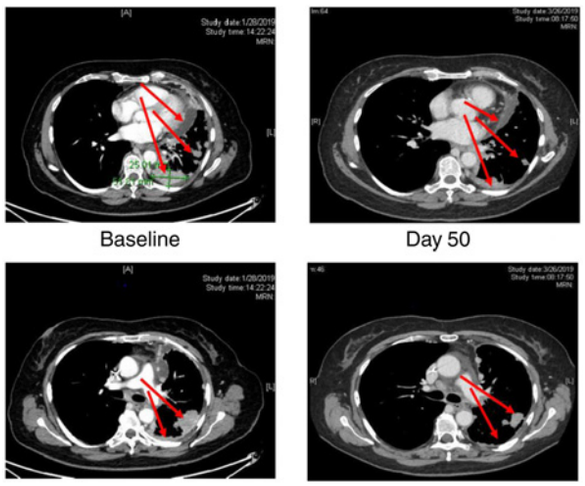


Figure 4.
Best patient response (cohort 5). Baseline scans on left, day 50 scans on right. Target lesions highlighted by red arrows, showing a 22% reduction by RECISTv1.1.

Authors' Disclosures

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Authors' Contributions

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