Abstract 8304: Phase 1b, Open Label, Multicenter Study of Inhaled DV281, a Toll-like Receptor 9 Agonist, in Combination with Nivolumab in Patients with Second- or Third-Line Advanced or Metastatic Non Small Cell Lung Cancer (NCT03326752)

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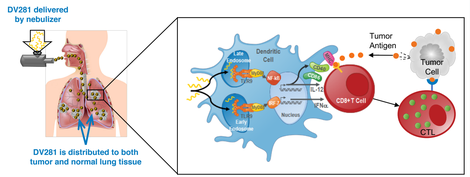
BACKGROUND

- Cytidine phosphoguanosine oligodeoxynucleotide-oligonucleotides (CpG-ODNs) are synthetic analogs of microbial DNA. C-class CpG-ODN (DV281 and SD-101) optimally activate toll-like receptor 9 (TLR9) to induce type I interferon (IFN) production and stimulate the maturation of dendritic cells to antigen-presenting cells.[1]
- Activation of dendritic cells through TLR9 in the presence of tumor antigens generates potent T cell-mediated anti-tumor immunity and can substantially improve the response to PD-1 blockade in mouse tumor models.[2,3]
- Intratumoral delivery of the CpG-ODN, SD-101 combined with pembrolizumab shows significant clinical efficacy in advanced melanoma (NCT02521870).[4]
- Many tumor types are not amenable to multiple local injections, with lung cancers being a clear example; therefore, it would be optimal to identify alternate modes of localized delivery of TLR9 agonists.
- The combination of an inhaled CpG-ODN with systemic PD-1 blockade can induce complete clearance of lung tumors as well as distant metastases and provide a long-term survival benefit in mouse models of lung cancer.[5]
- DV281 is an investigational CpG-ODN optimized for delivery to primary lung tumors and lung metastases via a nebulizer (Figure 1). In this phase 1b clinical study (NCT03326752), the safety, preliminary anti-tumor efficacy, and target engagement of inhaled DV281, in combination with the anti-PD-1 checkpoint inhibitor nivolumab, are being assessed for the treatment of patients with advanced non-small cell lung cancer (NSCLC).

Figure 1. DV281 is Delivered to the Lung via Inhalation, where it can Stimulate Tumor-killing Cytotoxic T Lymphocytes (CTL) by Direct Actions on Antigen-presenting Dendritic Cells



MHC: Major histocompatibility complex; IL-12: Interleukin 12; INFα: Interferon alpha;

METHODS

- **Phase 1b Dose Escalation of DV281:**
  - 3+3 design (five cohorts)
  - Staggered dosing
  - Intra-subject dose escalation
  - DLT Period = 28 days
- **Patients:**
  - Second- or third-line NSCLC
  - At least one measurable lung lesion
  - Anti-PD-1/L1 treatment experienced or naïve
- **Study Treatment:**
  - Investigational safety treatment regimen for DV281, administered via inhalation weekly for eight weeks followed by a five-week break and then every two weeks for another 24 weeks
  - Nivolumab is administered by I.V. (240 mg) every two weeks beginning on week three
- **Primary Endpoints:**
  - Safety and tolerability
- **Secondary Endpoints:**
  - Pharmacodynamics and clinical response by RECIST v1.1

Figure 2. Treatment Schema

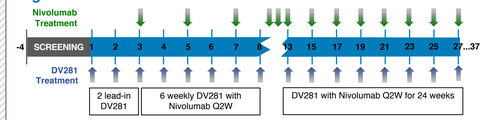


Figure 3. Dose Escalation Schema

	DV281 Monotherapy Lead-In		DV281 + Nivolumab
	Dose 1	*Dose 2*	*Doses 3, on*
Cohort 5 (N = 2)*	15.0 mg	25.0 mg	25.0 mg
Cohort 4 (N = 7)	10.0 mg	15.0 mg	15.0 mg
Cohort 3 (N = 7)	3.0 mg	10.0 mg	10.0 mg
Cohort 2 (N = 3)	1.0 mg	3.0 mg	3.0 mg
Cohort 1 (N = 4)	1.0 mg	1.0 mg	1.0 mg

* Dose escalation study is ongoing

BASELINE CHARACTERISTICS

Table 1. Baseline Patient and Disease Characteristics

Characteristics	Cohort 1 (N = 4)	Cohort 2 (N = 3)	Cohort 3 (N = 7)	Cohort 4 (N = 7)	Cohort 5 (N = 2)	Total (N = 23)
Median age, years (range)	64.0 (27, 70)	67.0 (59, 67)	68.0 (44, 85)	56.0 (49, 78)	74.5 (72, 77)	67.0 (27, 85)
Male, n (%)	1 (25)	1 (33.3)	4 (57.1)	5 (71.4)	0	11 (47.8)
ECOG PS, n (%)						
0	0	2 (66.7)	4 (57.1)	0	0	6 (26.1)
1	4 (100)	1 (33.3)	3 (42.9)	7 (100)	2 (100)	17 (73.9)
Histology:						
Squamous	2 (50)	1 (33.3)	1 (14.3)	2 (28.6)	1 (50)	7 (30.4)
Non-squamous	2 (50)	2 (66.7)	6 (85.7)	5 (71.4)	1 (50)	16 (69.6)
Stage at screening, n (%)						
IIIA	0	0	2 (28.6)	2 (28.6)	0	4 (17.4)
IIIB	1 (25)	0	1 (14.3)	1 (14.3)	0	3 (13)
IV	3 (75)	3 (100)	4 (57.1)	4 (57.1)	2 (100)	16 (69.6)
Missing	0	0	0	0	0	0
PD-L1 expression						
Positive	3 (75)	1 (33.3)	4 (57.1)	4 (57.1)	1 (50)	13 (56.5)
Negative	1 (25)	2 (66.7)	3 (42.9)	3 (42.9)	1 (50)	10 (43.5)
Oncogenic mutations						
KRAS	0	0	1 (14.3)	1 (14.3)	0	2 (8.7)
EGFR	1 (25)	0	0	1 (14.3)	0	2 (8.7)
HER2	0	1 (33.3)	0	0	0	1 (4.3)
ALK	0	0	0	0	0	0
BRAF	0	0	1 (14.3)	0	0	1 (4.3)

ECOG PS = Eastern Cooperative Oncology Group performance status

Table 2. Previous Treatments

Characteristics	Total (N = 23)
Prior lines of therapy, n (%)	
1	12 (52)
2	11 (48)
Prior radiotherapy to lung, n (%)	15 (65.2)
Prior systemic therapy, n (%)	
Chemotherapy only	3 (13)
Checkpoint inhibitor (CPI)	20 (87)
CPI + Chemotherapy	17 (74)
CPI only	3 (13)
Best response to previous anti-PD-1/PD-L1 therapy, n (%)	
Complete response	0
Partial response	1(4.3)
Stable disease	10 (43.5)
Progressive disease	4 (17.4)
NA	5 (21.7)

RESULTS

Table 3. Overview of Treatment-Emergent Adverse Events (TEAE)

Event, n (%)	1 mg (N = 4)	3 mg (N = 3)	10 mg (N = 7)	15 mg (N =7)	25 mg (N = 2)	Total (N = 23)
TEAE	4 (100)	3 (100)	7 (100)	7 (100)	1 (50)	22 (95.7)
Grade 1-2	4 (100)	3 (100)	7 (100)	7 (100)	1 (50)	22 (95.7)
Grade 3-4	2 (50)	1 (33.3)	3 (42.9)	1 (14.3)	0	7 (30.4)
Grade 5	0	0	0	0	0	0
Treatment-related AE	0	3 (100)	5 (71.4)	5 (71.4)	0	13 (56.5)
Grade 1-2	0	3 (100)	5 (71.4)	5 (71.4)	0	13 (56.5)
Grade 3-4	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0
Serious TEAE	1 (25)	0	2 (28.6)	1 (14.3)	0	4 (17.4)
Grade 1-2	0	0	1 (14.3)	0	0	1 (4.3)
Grade 3-4	1 (25)	0	2 (28.6)	1 (14.3)	0	4 (17.4)
Grade 5	0	0	0	0	0	0

Table 4. Safety Summary

Event, n (%)	Total (N = 23)
Any Treatment-related AE (Grade 1–2)	13 (56.5)
Chills	4 (17.4)
Myalgia	1 (4.3)
Influenza-like symptoms	1 (4.5)
Fatigue	3 (13.0)
Rash	3(13.0)
Pruritus	6 (26.1)
Angioedema	1 (4.3)
Vomiting	1 (4.3)
Diarrhea	3 (13.0)
Any irAEs	0
AEs leading to d/c of either or both drugs	1 (4.3)
SAEs	4 (17.4)
Death (treatment-related)	0

Table 5. Best Overall Response for ITT Population by RECIST

Characteristics	Cohort 1 (N = 4)	Cohort 2 (N = 3)	Cohort 3 (N = 7)	Cohort 4 (N = 7)	Cohort 5 (N = 2)	Total (N = 23)
Objective response rate, n	0	0	0	0	0	0
Best overall response, n (%)						
Complete response	0	0	0	0	0	0
Partial response	0	0	0	0	0	0
Stable disease	2 (50)	2 (66.7)	2 (28.6)	3 (42.9)	1 (50.0)	10 (43.5)
Progressive disease	1 (25)	1 (33.3)	5 (71.4)	3 (42.9)	0	10 (43.5)
Not evaluable	1 (25)	0	0	1 (14.3)	1 (50.0)	3 (13.0)
Duration of stable disease (Days)						
n	2	2	2	3	1	10
Mean (SD)	231.5 (24.75)	123.5 (0.71)	46 (21.21)	95.7 (30.14)	49	113.8 (70.83)
Median	231.5	123.5	46	99	49	111.0
Min, Max	214, 249	123, 124	31, 61	64, 124	49, 49	31, 249

Figure 4. Patient Cohort 5 (DV281 25 mg): Example of Tumor Reduction

Non squamous, Stage 4

Previous treatment:
- First line: carboplatin – pemetrexed
- Pemetrexed maintenance
- Second line: pembrolizumab: 4 months
- Best response: PD
- Severe dyspnea and pain at enrollment

At day 50:
- Dramatic clinical improvement (normal breathing, disappearance of pain)
- Global SD on the CT scan

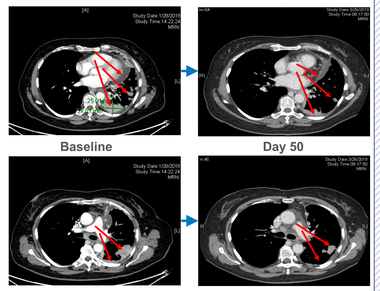


Figure 5. Individual Tumor Analysis Reveals Anti-tumor Effects in All Cohorts; Examples of Patients That Have Progressed After anti-PD-1/PD-L1

Patient 1: Cohort 1: 1 mg
- Tumor status before enrollment
  - PD: lymph node (LN), soft tissue metastasis (ST), and occurrence of adrenal metastasis (Adr)
  - Primary tumor (PT): SD
- Tumor status on treatment
  - Initial progression of PT then SD
  - Control of soft tissue metastasis and adrenal metastasis
  - Delayed and continuous progression of lymph node
  - Global SD then PD at 8 months based on lymph node only
  - Treatment stopped

Reduction of Tumor Growth: Tumor Doubling Times (TDT) before and after enrollment:
- Soft tissue lesion and adrenal metastasis: 1.3 months before enrollment and several years after
- Lymph node: TDT = 1.3 months before enrollment, TDT = 6 months after enrollment

Patient 2: Cohort 2: 3 mg
- Tumor status before enrollment
  - Primary tumor (Right Upper Lobe), supraclavicular lymph node, mediastinal LN, multiple bone metastases
  - Confirmed PD
- Tumor status on treatment
  - Stable disease at 4 months
  - PD at 6 months, on bone metastases, target lesion controlled
  - Treatment stopped

Reduction of Tumor Growth: Comparison of the TDT before and after enrollment:
- Primary tumor: TDT initially at 28 months then becomes negative

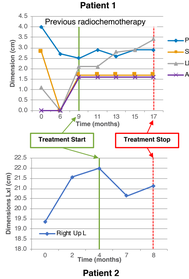
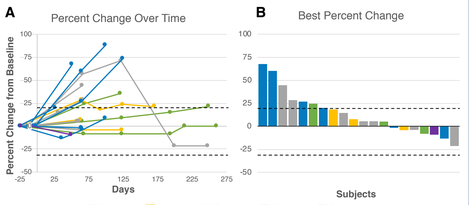
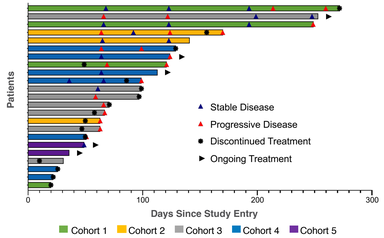


Figure 6. Change from Baseline in Target Lesion(s) for ITT Population



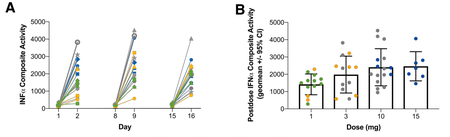
- Signs of anti-tumor activity was noted in two patients with prolonged stable disease (reversal of the pace of disease) and whose time on study treatment exceeded the time on prior checkpoint inhibitors

Figure 7. Subject Response History and Current Status in the Dose Escalation, Intent-to-Treat (ITT) Population



PHARMACODYNAMIC ACTIVITY

Figure 8. Dose-Dependent Target Engagement by Inhaled DV281 Has Been Confirmed At All Dose Levels Tested



- Induction of IFN-regulated genes in the blood is indicative of target engagement in the lung upon TLR9 stimulation.
  - **A.** Composite scores of IFN activity were calculated in pre-dose (days 1,8, 15) and respective post-dose (days 2,9,16) blood samples for each patient.
  - **B.** Post-dose composite activity for each patient by dose.

CONCLUSIONS

- In this safety study, two doses of DV281 monotherapy followed by combination with nivolumab was well tolerated. No immune-related adverse events such as pneumonitis have been reported
- Inhalation of DV281 leads to dose-dependent target engagement as measured by induction of IFN-regulated genes at all evaluated dose levels
- DV281 plus nivolumab demonstrates early signs of antitumor activity in heavily pretreated patients (87% received prior CPI ± chemotherapy)
  - Dramatic clinical improvement and clear tumor shrinkage at day 50 CT scan in a patient treated at 25 mg who was progressing on pembrolizumab
  - Prolonged SD (4–8 months) have been observed in the first two cohorts which have sufficient duration of follow-up
  - Clear control of target lesions as measured on CT scans and slowing down of tumor growth with significantly extended tumor doubling time.
- The dose escalation phase of the study is ongoing; expansion phase cohorts are being planned

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