HHS Public Access

Author manuscript

Clin Cancer Res. Author manuscript; available in PMC 2022 December 01.

Published in final edited form as:

Clin Cancer Res. 2022 June 01; 28(11): 2313–2320. doi:10.1158/1078-0432.CCR-21-2742.

Phase I study of taminadenant (PBF509/NIR178), an adenosine 2A receptor antagonist, with or without spartalizumab, in patients with advanced non-small cell lung cancer

Alberto A. Chiappori[1], **Ben Creelan**[1], **Tawee Tanvetyanon**[1], **Jhanelle E. Gray**[1], **Eric B. Haura**[1], **Ram Thapa**[2], **Margaret L. Barlow**[3], **Zhihua Chen**[2], **Dung Tsa Chen**[2], **Amer A. Beg**[1,3], **Theresa A. Boyle**[4], **Julio Castro**[5], **Liza Morgan**[6], **Erick Morris**[7], **Mehreteab Aregay**[6], **Felipe K. Hurtado**[6], **Luigi Manenti**[7], **Scott Antonia**[8]

[1]Department of Thoracic Oncology, Moffitt Cancer Center, Tampa, FL

[2]Department of Biostatistics and Bioinformatics, Moffitt Cancer Center, Tampa, FL

[3]Department of Immunology, Moffitt Cancer Center, Tampa, FL

Corresponding author: Alberto A. Chiappori, Department of Thoracic Oncology, Moffitt Cancer Center, Tampa, FL 33612, Alberto.Chiappori@moffitt.org, Tel: +1-888-663-3488.

Authors' Contributions

Alberto A. Chiappori: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Writing - Original Draft, Writing - Review & Editing, Supervision, Project administration, Funding acquisition. **Ben Creelan:** Investigation, Resources, Data Curation, Writing - Review & Editing. **Tawee Tanvetyanon:** Investigation, Resources, Writing - Review & Editing. **Jhanelle E. Gray:** Methodology, Resources, Writing - Original Draft, Writing - Review & Editing, Project administration. **Eric B. Haura:** Resources, Writing - Review & Editing. **Ram Thapa:** Formal analysis, Writing - Review & Editing, Visualization. **Margaret L. Barlow:** Formal analysis, Writing - Review & Editing. **Zhihua Chen:** Formal analysis, Writing - Review & Editing. **Dung Tsa Chen:** Formal analysis, Writing - Review & Editing. **Amer A. Beg:** Methodology, Investigation, Writing - Review & Editing, Project administration, Funding acquisition. **Theresa A. Boyle:** Validation, Formal analysis, Investigation, Writing - Review & Editing, Visualization. **Julio Castro:** Conceptualization, Resources, Writing - Review & Editing, Project administration. **Liza Morgan:** Data Curation, Writing - Original Draft, Writing - Review & Editing, Visualization, Project administration. **Erick Morris:** Conceptualization, Methodology, Data Curation, Writing - Original Draft, Writing - Review & Editing, Supervision, Project administration. **Mehreteab Aregay:** Methodology, Software, Validation, Formal analysis, Writing – Review & Editing, Visualization. **Felipe K. Hurtado:** Conceptualization, Formal analysis, Writing - Original Draft, Writing - Review & Editing, Visualization. **Luigi Manenti:** Conceptualization, Validation, Writing - Original Draft, Writing - Review & Editing, Supervision, Funding acquisition. **Scott Antonia:** Conceptualization, Methodology, Validation, Investigation, Writing - Original Draft, Visualization, Supervision, Project administration.

Disclosure:

Alberto A. Chiappori reports grants from LUNGevity Foundation during the conduct of the study; personal fees outside the submitted work from Merck, Genentech, Takeda, Blue Print Medicines and Celgene for Speaker's Bureaus; personal fees outside the submitted work from AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Jazz, Novartis, and Pfizer for Advisory Boards; and research funding outside the submitted work from AstraZeneca, Bristol-Myers Squibb, and Novartis. **Ben Creelan** is an advisor/consultant with AbbVie, Achilles, Celgene, E.R. Squibb & Sons, Gilead Sciences, GlaxoSmithKline, KSQ Therapeutics, and Xilio Therapeutics; sits on the Speaker's Bureau for AstraZeneca, E.R. Squibb & Sons, Foundation Medicine, Hoffman-LaRoche, and Takeda; and reports contacted/support research grants from Adaptive Biotechnologies, Iovance Biotherapeutics, and Prometheus. **Jhanelle E. Gray** reports research grants outside the submitted work from AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Genentech, G1 Therapeutics, Merck, Novartis, Pfizer, and Ludwig Institute of Cancer Research; personal fees for consultant/advisory roles outside the submitted work from AstraZeneca, Blue Print Medicines, Bristol-Myers Squibb, EMB Serono-Merck, Inivata, Merck, and Novartis. **Eric B. Haura** reports personal fees for consultancy outside the submitted work from Janssen and Amgen. **Amer A. Beg** reports consulting roles outside the submitted work with Memgen. **Julio Castro** reports employment by Palobiofarma. **Liza Morgan** reports employment by Novartis. **Mehreteab Aregay and Felipe K. Hurtado** report employment with Novartis during the study period. **Erick Morris and Luigi Manenti** report employment by Novartis and holding Novartis stocks/shares. **Scott Antonia** reports institutional research funding from Novartis; consulting/advisory roles for Achilles Therapeutics, Amgen, AstraZeneca, Bristol-Myers Squibb, CBMG, Celsius, GlaxoSmithKline, Merck, Memgen, RAPT, Samyang Biopharma, and Venn; travel/accommodations/expenses from Achilles Therapeutics, Amgen, Bristol-Myers Squibb, Celsius, GlaxoSmithKline, Merck, and Rapt. **Tawee Tanvetyanon, Ram Thapa, Margaret L. Barlow, Zhihua Chen, Dung Tsa Chen, and Theresa A. Boyle** declare no conflict of interest.

[4]Department of Pathology, Moffitt Cancer Center, Tampa, FL

[5]Palobiofarma S.L., Navarra, Spain

[6]Novartis Pharmaceuticals Corporation, East Hanover, NJ

[7]Novartis Institutes for Biomedical Research, Cambridge, MA

[8]Duke Cancer Institute, Durham, NC

Abstract

Purpose—The adenosine 2A receptor (A2AR) mediates the immunosuppressive effects of adenosine in the tumor microenvironment and is highly expressed in non-small cell lung cancer (NSCLC). Taminadenant (PBF509/NIR178) is an A2AR antagonist able to reactivate the antitumor immune response.

Experimental Design—In this phase I/Ib, dose-escalation/expansion study, patients with advanced/metastatic NSCLC and ≥1 prior therapy received taminadenant (80–640 mg; orally; twice-daily) with or without spartalizumab (anti-programmed cell death-1; 400 mg; intravenously; every four weeks). Primary endpoints: safety, tolerability, and feasibility of the combination.

Results—During dose escalation, 25 patients each received taminadenant alone or with spartalizumab; 19 (76.0%) and 9 (36.0%) had prior immunotherapy, respectively. Dose-limiting toxicities (all Grade 3) with taminadenant alone were alanine/aspartate aminotransferase increase and nausea (n=1 [4.0%] each; 640 mg) and in the combination group were pneumonitis (n=2 [8.0%]; 160 and 240 mg), fatigue and alanine/aspartate aminotransferase increase (n=1 [4.0%] each; 320 mg); pneumonitis cases responded to steroids rapidly and successfully. Complete and partial responses were observed in one patient each in the single-agent and combination groups; all immunotherapy-naïve. In the single-agent and combination groups, seven and 14 patients experienced stable disease; seven and six patients were immunotherapy-pretreated, respectively.

Conclusions—Taminadenant, with and without spartalizumab, was well tolerated in patients with advanced NSCLC. The maximum tolerated dose of taminadenant alone was 480 mg twice-daily, and 240 mg twice-daily plus spartalizumab. Efficacy was neither a primary or secondary endpoint; however, some clinical benefit was noted regardless of prior immunotherapy or programmed cell death ligand-1 status.

Keywords

Adenosine signaling; carcinoma; non-small cell lung; taminadenant; programmed cell death ligand-1; spartalizumab

Introduction

Non-small cell lung cancer (NSCLC) accounts for 84% of all lung cancer diagnoses in the USA (1,2). Current treatment guidelines for NSCLC include immune checkpoint inhibitors (CPI), targeted therapies that depend on the presence of genetic alterations, and chemotherapy (3,4). Immunohistochemical analysis of a variety of tumor types demonstrated high levels of adenosine 2A receptor (A2AR) expression in tumor cells and,

most notably, in lung adenocarcinomas (5). The adenosine pathway is a major inhibitory pathway in the tumor microenvironment that contributes to tumor evasion from the immune response (6,7). High levels of adenosine in the tumor microenvironment downregulate the functions of infiltrating immune cells, preventing the destruction of tumor cells (6).

Taminadenant (PBF509/NIR178) is an oral, small-molecule, potent and selective A2AR antagonist. *In vitro* experiments in cells transfected with A2AR demonstrated the selective binding of taminadenant to A2AR, resulting in inhibition of cyclic adenosine monophosphate accumulation (8). Taminadenant administration significantly reduced tumor growth in mouse xenograft models (8). In combination with immune checkpoint inhibition, A2AR blockade may enhance activation of the immune system and effector function (9). The CPI spartalizumab (PDR001) is a monoclonal antibody that binds to programmed cell death-1 (PD-1), blocking its interaction with programmed cell death ligand-1 (PD-L1), to restore effector T-cell function (10). Herein we report results from the first-in-human phase I/Ib study of taminadenant both as a single agent and in combination with spartalizumab in patients with advanced NSCLC (NCT02403193).

Patients and Methods

Study design, treatment, and objectives

This was a phase I/Ib dose-escalation and expansion study of taminadenant either as a single agent or in combination with spartalizumab in patients with advanced NSCLC. Patients in the single-agent group received taminadenant in escalating doses of 80 mg, 160 mg, 320 mg, 480 mg, and 640 mg, orally, twice-daily (BID). Patients in the combination group received a fixed dose of spartalizumab (400 mg), intravenously, once every four weeks (Q4W) and escalating doses of taminadenant (160 mg, 240 mg, or 320 mg), orally, BID. The starting dose of taminadenant was based on safety, tolerability, and pharmacokinetics (PK) in animal studies and first-in-human trials of healthy volunteers, potency in *in vitro* binding assays and cellular assays, and efficacy in preclinical models. Following analysis of the initial safety and PK data in the earlier enrolled single-agent group, lower dose levels of taminadenant were planned when administered in combination with spartalizumab. On Cycle 1 Day 1 only one dose of taminadenant was administered in both treatment groups to allow for assessment of the 0–24-hour PK profile; the BID regimen began on Cycle 1 Day 2. Dose escalation was according to a modified 3 + 3 design. Treatment was administered until unacceptable toxicity, confirmation of progressive disease (PD), or patient/physician decision to discontinue. Patients who discontinued treatment were followed until withdrawal of informed consent, death, or refusal to further follow-up. Taminadenant dose reductions were permitted in case of toxicity; dose reductions of spartalizumab were not permitted, however, spartalizumab dosing delays were allowed.

The primary objectives of the dose-escalation portion of the study were to determine the dose-limiting toxicities (DLTs) and maximum tolerated dose (MTD) of taminadenant in combination with spartalizumab and to determine the PK profile of the combination. Secondary objectives included preliminary efficacy of taminadenant with or without spartalizumab, and evaluation of the corresponding safety and tolerability. Evaluation of

the association between response to taminadenant with or without spartalizumab and tumor immunogenicity prior to treatment was an exploratory objective.

Patient population

Adult patients with a histologic or cytologic diagnosis of advanced or metastatic NSCLC with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 were eligible. Although no maximum number of prior lines of therapy was specified, participating patients required at least one prior line of therapy for their disease before enrolling on the study. Patients with a sensitizing *EGFR* mutation (exon 19 deletion or L858R) or who were positive for *ALK* rearrangement were eligible if they had failed prior targeted therapy with a tyrosine kinase inhibitor or chemotherapy. Patients had measurable disease at screening and may have received prior immunotherapy including anti-cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), anti-PD-1, and anti-PD-L1 CPIs, either as single agents or in combination. Patients with current or prior use of immunosuppressive medication within 28 days before the first dose of spartalizumab were excluded, with the exception of corticosteroids ≤10 mg/day prednisone, or equivalent. Patients were required to have adequate organ and marrow function. Any patient with symptomatic or uncontrolled brain metastases requiring concurrent treatment were also excluded from this study. Patients with active or prior documented autoimmune disease within the past 2 years (excluding vitiligo, Grave's disease, or psoriasis not requiring systemic treatment), or a history of hypersensitivity to spartalizumab or taminadenant were excluded. Only female patients of non-reproductive potential (post-menopausal, hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or of child-bearing potential with a negative serum pregnancy test upon study entry and using two highly effective methods of contraceptive were enrolled. Sexually active male patients, including those with prior vasectomy, were required to use a condom during intercourse throughout the study and for 150 days after stopping spartalizumab therapy. Patients with a mean QT interval corrected for heart rate (QTc) of 470 ms or longer, calculated from three electrocardiograms (ECGs) ≥1 minute apart using Bazett's Correction were not permitted. Patients were also excluded if they had acute myocardial infarction or unstable angina pectoris <3 months prior to study entry, and history of primary immunodeficiency, allogeneic organ transplant, tuberculosis, or leptomeningeal carcinomatosis.

Assessments

Regular safety assessments were performed throughout the study including vital signs, ECOG performance status, chemistry panel, and cardiac assessments. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Radiographic assessments were performed every 8 weeks up to 48 weeks, then every 12 weeks thereafter until disease progression or patient withdrawal. Tumor response was assessed per Response Evaluation Criteria In Solid Tumors v1.1 (RECIST v1.1) (11). A fresh or archival tumor biopsy sample was collected from each patient prior to starting treatment and post-dose on Cycle 2 Day 15 (±7 days). A further optional tumor biopsy was obtained upon disease progression from patients who initially responded to study treatment. PD-L1 tumor proportion score was measured by immunohistochemistry (IHC) using the 22C3 pharmDx kit. Blood samples for taminadenant

PK assessments were collected on Day 1, 2, 8, and 9 during Cycle 1, Day 1 and 2 of Cycle 2, and Day 1 of Cycles 3–6. Plasma concentrations of taminadenant were measured by liquid chromatography-tandem mass spectrometry.

Statistical analysis

The MTD was defined as the highest dose level at which less than one-third of patients experienced a DLT. The period for evaluation of DLTs for taminadenant alone was during the first 28 days of the treatment cycle (Cycle 1) and, for taminadenant in combination with spartalizumab, during the first 56 days of the treatment cycle (Cycles 1 and 2). DLTs and the modified 3+3 design are defined in the supplementary data A and B. Determination of the MTD required safety data from at least six evaluable patients and was defined as the highest dose level at which less than one-third of patients experience a DLT in Cycle 1.

Safety was evaluated in all patients who received at least one dose of taminadenant, with or without spartalizumab. Efficacy analysis was based on the intent-to-treat principle and included all patients who received at least one dose of either taminadenant or spartalizumab. Overall response rate (ORR) and disease control rate (DCR) were calculated based on the number of evaluable patients through binomial distribution with a two-sided 95% confidence interval (CI). Overall survival (OS) and progression-free survival (PFS) were estimated using the Kaplan–Meier method; PFS was measured from the start date of treatment to the first occurrence of disease progression per RECIST v1.1 or death on study from any cause, and OS from the start date of treatment to death on study from any cause.

Biomarker studies

Biomarker studies were mostly performed on the taminadenant plus spartalizumab group. CD8/CD33 IHC staining and analysis was performed as in our previous studies (12). Briefly, a 0–3 scale was used to determine the density of $CD8^+$ T cells and $CD33^+$ myeloid cells in tissue sections. A NanoString PanCancer Immune Profiling Panel was utilized for gene-expression studies. Adenosine pathway-regulated gene-expression signature activity (13) (IL1B, PTGS2, and CXCL1, 2, 3, 5, 6, and 8) was tested on pre-treatment and on-treatment biopsy NanoString data in association with patient survival (months from on study to expired/last date known alive).

Ethical oversight

This study was conducted in accordance with the Declaration of Helsinki and was performed in compliance with Good Clinical Practice guidelines. The protocol and all amendments were reviewed and approved by an Independent Ethics Committee or Institutional Review Board at each site. All patients provided informed written consent prior to study start.

Data availability

Access to patient-level data cannot be provided if there is a reasonable likelihood that individual patients could be re-identified. Phase 1 studies, by their nature, present a high risk of patient re-identification; therefore, patient individual results for phase 1 studies cannot be shared. In addition, clinical data, in some cases, have been collected subject to contractual or consent provisions that prohibit transfer to third parties. Such restrictions may

preclude granting access under these provisions. Where co-development agreements or other legal restrictions prevent companies from sharing particular data, companies will work with qualified requestors to provide summary information where possible.

Results

Patient characteristics and disposition

The study opened and began enrolling patients on September 29, 2015, with the first patient enrolled on October 15, 2015. The last patient was enrolled on June 15, 2017 (18 months later). As of January 15, 2020, 50 patients had received taminadenant alone (n=25) or in combination (n=25) with spartalizumab. In the taminadenant single-agent group, 24 (96.0%) patients discontinued due to disease progression (n=15; 60.0%), patient withdrawal (n=4; 16.0%; due to withdrawal of informed consent [n=3], or no longer wishing to participate [n=1]), adverse events (n=3; 12.0%), and death (n=2; 8.0%). In the taminadenant plus spartalizumab group, 24 (96.0%) patients discontinued due to disease progression (n=13; 52.0%), adverse events (n=5; 20.0%), death (n=4; 16.0%), and patient withdrawal (n=2; 8.0%; due to withdrawal of informed consent). One patient in each group remained on treatment at data cut-off. Baseline patient characteristics are shown in Table 1. In the taminadenant single-agent group, most patients had received prior immunotherapy (76.0%); 52.0% and 24.0% had received prior anti-PD-1 and anti-PD-L1 CPIs, respectively. Of patients in the taminadenant plus spartalizumab group, 36.0% had received prior immunotherapy; 28.0% with anti-PD-1 and 8.0% with anti-PD-L1 CPIs. There were six on-study deaths; none were related to study treatment. The two (8.0%) on-study deaths in the taminadenant single-agent group were due to disease progression (n=1) and cause not documented (n=1). The four (16.0%) on-study deaths in the taminadenant plus spartalizumab group were due to disease progression (n=3) and an adverse event (n=1; as a complication from the underlying disease).

Pharmacokinetics

After a single oral dose, taminadenant was rapidly absorbed with maximum plasma drug concentration (C_{max}) reached after 0.5–3 hours (Fig. 1). Systemic exposure, as measured by C_{max} and area under the plasma concentration–time curve (AUC), increased with escalating doses in a more-than-proportional manner after both single and multiple doses from 80 mg to 640 mg (Supplementary Table S1). Large inter-individual variability in exposure was observed, most notably after single-dose administration and at doses less than 480 mg BID. Repeated daily doses of taminadenant resulted in a moderate accumulation (by approximately 3-fold) after 1 week, relative to a single dose. Following multiple-dose administration, the effective half-life at steady-state ranged from 7 to 61 hours across dose levels. The apparent volume of distribution (V_d/F) ranged from 114 to 1522 L, suggesting that taminadenant has a large extravascular distribution to peripheral tissues. Taminadenant demonstrated dose- and time-dependent nonlinear PK; apparent clearance (CL/F) notably decreased upon repeated daily dosing, compared with that after a single dose, and decreased with increasing doses. This finding suggests saturation in taminadenant metabolism and/or oral bioavailability. Acknowledging the large inter-individual variability

in C_{max} and AUC, there were no notable differences in taminadenant PK between the single-agent and combination group.

Safety

All patients across the taminadenant single-agent and combination treatment groups reported at least one adverse event, regardless of causality (Supplementary Table S2). Treatment-related adverse events (TRAEs) of any grade were reported in 21 (84.0%) and 15 (60.0%) patients treated with taminadenant single agent and taminadenant plus spartalizumab, respectively (Supplementary Table S3). The most common TRAEs reported in at least 10% of patients in the taminadenant single-agent group were nausea (n=11; 44.0%), gastroesophageal reflux disease (n=6; 24.0%), vomiting (n=5; 20.0%), and fatigue (n=5, 20.0%; Fig. 2A). In patients treated with taminadenant plus spartalizumab, the most common TRAEs reported in at least 10% of patients were nausea (n=7; 28.0%), increased aspartate aminotransferase (AST; n=5; 20.0%), increased alanine aminotransferase (ALT; n=5; 20.0%), increased lipase (n=4; 16.0%), and fatigue (n=4; 16.0%; Fig. 2B). Grade 3/4 TRAEs were reported in four (16.0%) patients who received taminadenant single agent and nine (36.0%) patients who received taminadenant plus spartalizumab. Common grade 3/4 TRAEs reported in at least two patients in the taminadenant plus spartalizumab group were increased AST (n=3; 12.0%), increased lipase (n=3; 12.0%), increased ALT (n=2; 8.0%), and pneumonitis (n=2; 8.0%); patients experiencing pneumonitis responded to steroids rapidly and successfully. No grade 3/4 TRAE was reported in more than one patient each treated with taminadenant single agent. Serious adverse events (SAEs) of any causality led to treatment interruption in one patient in the taminadenant single-agent group and two patients in the taminadenant plus spartalizumab group. SAEs thought to be related to treatment were reported in one patient in the taminadenant single-agent group (Grade 3 increased ALT and AST; taminadenant 640 mg) and in two patients in the taminadenant plus spartalizumab group (both Grade 3 pneumonitis; taminadenant 160 mg and 240 mg). The patient with Grade 3 increased ALT and AST recovered following regimen interruption. Both patients who experienced Grade 3 pneumonitis discontinued treatment (Supplementary Table S4).

Between both groups (taminadenant single agent and taminadenant plus spartalizumab), dose delays or interruptions occurred in 25 patients (13 patients in the taminadenant single-agent group and 12 patients in the taminadenant plus spartalizumab group). Overall, dose delays due to TRAEs were reported in five patients in the single-agent group and six patients in the taminadenant plus spartalizumab group.

There were two DLTs in the taminadenant single-agent group, both at the 640 mg dose level: Grade 3 ALT/AST increase (n=1) and Grade 3 nausea (n=1). DLTs in the taminadenant plus spartalizumab group were pneumonitis (n=2; taminadenant 160 mg and 240 mg), fatigue (n=1; taminadenant 320 mg), and ALT/AST increase (n=1; taminadenant 320 mg); all Grade 3. The MTD was declared as 480 mg BID for single-agent taminadenant and 240 mg BID taminadenant in combination with 400 mg spartalizumab Q4W.

Efficacy

At data cut-off, the respective DCRs and ORRs were 42.9% and 9.5% in the taminadenant single-agent group, and 66.7% and 8.3% in the taminadenant plus spartalizumab group (Table 2). Best overall responses in the taminadenant single-agent group were as follows: one (4.0%) patient had a complete response (CR), one (4.0%) patient experienced a partial response (PR), 7 (28.0%) patients had stable disease (SD), and 12 (48.0%) patients had PD as per RECIST v1.1 (Table 2). The patient who experienced a CR received 480 mg taminadenant with a duration of response of 1.1 months, additional patient information is included in the supplementary data C. The PR lasted for 6.4 months and was experienced by a patient who received taminadenant at the 80 mg dose level. Both patients in the taminadenant single-agent group who experienced a tumor response discontinued due to adverse events; the first had Grade 3 pneumonitis suspected to be treatment related that resolved 18 days later, and the second had Grade 2 dizziness that was unrelated to treatment. Of note, one patient treated with taminadenant single agent at 160 mg who experienced a best overall response of SD remains on treatment at data cut-off, with disease control lasting 36.7 months. All of the patients who experienced SD had received prior anti-PD-1/PD-L1 therapy prior to study entry (Fig. 3A). In the taminadenant plus spartalizumab group, one (4.0%) patient had a CR, one (4.0%) patient experienced a PR, 14 (56.0%) patients had SD, and eight (32.0%) patients had PD. The CR lasted for 15.9 months and was reported in a patient treated with 160 mg taminadenant plus spartalizumab who subsequently discontinued due to adverse events (patient case detailed in the supplementary data C). The patient who experienced a PR received 240 mg taminadenant plus spartalizumab and remains on treatment with response ongoing at data cut-off for 16.6 months. Of the 14 patients treated with taminadenant plus spartalizumab who experienced SD, six had received prior anti-PD-1/PD-L1 therapy (Fig. 3B). The median duration of exposure was 1.8 months (range: 0.1–12.0) in the taminadenant single-agent group and 2.3 months (range: 0.2–27.0) in the taminadenant plus spartalizumab group. In the taminadenant single-agent group, median estimates of OS and PFS were 9.7 months (95% CI: 7.7–22.1) and 3.9 months (95% CI: 1.8–8.7), respectively (Supplementary Fig. S1). Median estimates of OS and PFS in the taminadenant plus spartalizumab group were 5.4 months (95% CI: 3.3–20.8) and 2.8 months (95% CI: 1.9–5.6), respectively (Supplementary Fig. S1).

Biomarker analysis

Pre-treatment fresh or archival tumor biopsies were analyzed for baseline PD-L1 expression by IHC for 12 and 17 patients who also had best percentage change data in the taminadenant single-agent and taminadenant plus spartalizumab groups, respectively (Supplementary Fig. S2). Clinical activity of taminadenant with or without spartalizumab was observed irrespective of PD-L1 expression (Supplementary Fig. S2A and S2B).

Baseline (pre-treatment; n=9) and on-treatment (n=5) levels of $CD8^+$ T cells and $CD33^+$ myeloid were determined by IHC, as in our previous study (12), in biopsy tissue from the taminadenant plus spartalizumab group. No significant differences in pre-treatment vs. on-treatment levels of either cell population were seen (Supplementary Figs. S3A and S3B). Similarly, no clear trend in either cell type was seen in the five patients with both pre-treatment and on-treatment biopsies (Supplementary Figs. S3C and S3D).

NanoString gene-expression analysis was performed on 11 patients in the taminadenant plus spartalizumab group with paired fresh–frozen biopsies using the PanCancer Immune Profiling Panel. Genes differentially expressed upon treatment are shown in a volcano plot in Supplementary Fig. S4. Notably, genes implicated in IFNγ and inflammatory cytokine signaling (e.g., *IRF1*, *GBP2*, and *JAK2*) were significantly upregulated after treatment, suggesting treatment-induced immune activation in the tumor microenvironment. A recent study showed that clinical responses to the A2AR inhibitor, ciforadenant, in renal cell cancer were associated with an adenosine pathway-regulated gene-expression signature in pretreatment tumor biopsies (13). In the 11 taminadenant plus spartalizumab group patients with gene-expression data, there were nine SDs, one PR and one PD, which made it difficult to assess association of signature activity with response. Instead, we used patient survival to determine potential association with adenosine pathway activity (time from on study to expiration). However, these studies showed no clear correlation of signature activity with survival in either the pre-treatment or on-treatment biopsies (Supplementary Fig. S5).

Discussion

In this phase I/Ib, dose-escalation/expansion study, DLTs were reported at the 640 mg dose level for taminadenant single agent, and at the taminadenant 160 mg, 240 mg, and 320 mg dose levels in the taminadenant plus spartalizumab group. The MTD was declared as 480 mg BID for single-agent taminadenant and 240 mg BID for taminadenant in combination with 400 mg spartalizumab Q4W.

Taminadenant therapy was well tolerated, both as a single agent and in combination with spartalizumab; only three (12.0%) and five (20.0%) patients discontinued due to adverse events in the taminadenant single-agent and taminadenant plus spartalizumab groups, respectively. The most common adverse events thought to be related to study treatment in the taminadenant single-agent group were nausea, gastroesophageal reflux disease, fatigue, and vomiting. In the taminadenant plus spartalizumab group, the most common adverse events thought to be related to study treatment were nausea, increased liver enzymes (ALT and AST), fatigue, and increased lipase. The observed adverse events are consistent with the known safety profile of spartalizumab and the class effect of immune CPIs (10). Safety results, including the type and frequency of TRAEs, were also similar to the safety profile of another A2AR inhibitor, ciforadenant, in combination with the PD-L1 inhibitor, atezolizumab, in patients with renal cell cancer (14).

Taminadenant PK was characterized from 80 to 640 mg BID, both as a single agent and in combination with spartalizumab. Taminadenant exposure increased with dose in a more-than-proportional manner and exhibited high inter-patient variability. The variability in PK could, in part be, due to a small number of patients in each cohort (n=3–10). Throughout the dosing interval, taminadenant doses of 160 mg or higher achieved steady-state exposure that exceeded the *in vitro* binding affinity of taminadenant to human A2AR (12 nM or 3.67 ng/mL) (8).

In this study, nine (36.0%) and 16 (64.0%) patients achieved disease control in the taminadenant single-agent and taminadenant plus spartalizumab groups, respectively. One

patient in each group achieved tumor reduction consistent with a CR, and one patient in each group experienced a PR. CR and PR were only observed in patients who had not received prior anti-PD-1/PD-L1 therapy. Among 12 patients experiencing some tumor shrinkage (Fig. 3A and B), only 3 patients were previously exposed to immune CPIs; however, all patients in the taminadenant single-agent group and six of 14 patients in the taminadenant plus spartalizumab group who experienced SD had received anti-PD-1/PD-L1 therapy prior to study entry. Whilst clinical activity of taminadenant with or without spartalizumab was observed across the range of PD-L1 baseline expression; the small sample size and insufficient number of paired pre- and post-treatment tumor samples precludes any conclusions. It should be noted, however, that in the completed follow-up Phase II study (NCT03207867) wherein the objective was the optimization of the dosing schedule in a cohort of patients with NSCLC with similar eligibility parameters to the Phase 1/1b study, it was concluded that the combination of taminadenant plus spartalizumab did not show sufficient activity in patients with NSCLC. As such, the combination together with the changes in the standard of care, will not be pursued in this indication (15). It should be noted that the aim of this study was to evaluate the safety and tolerability of taminadenant alone and in combination with spartalizumab and the feasibility of concurrent administration of spartalizumab and taminadenant. This study was not planned with a primary efficacy endpoint and further studies are required to investigate the efficacy of taminadenant with or without spartalizumab and confirm its utility in advanced NSCLC. No significant change in the level of $CD8^+$ T-cells was associated with taminadenant plus spartalizumab treatment, although gene-expression studies indicated an increase in immune activity in tumors. We also did not find an association between an adenosine pathway signature and survival in patients treated with taminadenant plus spartalizumab.

A number of studies are ongoing investigating A2AR antagonists as monotherapies or in various combinations in indications including renal cell carcinoma, prostate cancer and NSCLC. Efficacy appears to be limited for A2AR antagonist monotherapy, but is enhanced in combinations with anti-PD-(L)1 agents (2,13,16). Recent preclinical data have also shown that combining A2AR antagonists with CD73 antagonists may improve therapeutic response (2,17). This combination may play an important role in the treatment of patients with *EGFR*-mutant NSCLC given the observed increase in CD73 expression in *EGFR*-mutant adenocarcinomas compared with those with wild-type *EGFR* (18,19). Taminadenant is currently under investigation in several clinical trials including in combination with NZV930 (an anti-CD73 monoclonal antibody) or spartalizumab for patients with advanced malignancies including NSCLC, triple-negative breast cancer, pancreatic ductal adenocarcinoma, and non-Hodgkin lymphoma, and in combination with KAZ954 (an anti-ectonucleoside triphosphate disphosphohydrolase monoclonal antibody) in patients with advanced solid tumors (20,21).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors would like to acknowledge the support of the Clinical Trials Coordinators, Noemi Rodriguez Guadalupe and Rebecca DeVane, and the Clinical Trials Lab Core, Tony Neuger and Gustavo Luna at Moffitt Cancer Center. The authors also acknowledge services provided by the Molecular Genomics, Biostatistics and Bioinformatics Shared Resource, Tissue and Analytic Microscopy Cores at Moffitt Cancer Center, an NCI-designated Comprehensive Cancer Center (P30-CA076292).

Medical writing assistance was provided by Jenny Winstanley, PhD, of Articulate Science Ltd.

Financial support:

This study was funded by Novartis Pharmaceuticals Corporation who also provided funding for medical writing assistance and contributed to the decision to submit the article for publication, the LUNGevity Targeted Therapeutics Award (Grant number: 2014-07, 2014), and NIH R01CA201124 (Scott Antonia and Amer A. Beg). The sponsors had no involvement in study design or in the collection, analysis, and interpretation of data.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69(1):7–34 doi 10.3322/caac.21551. [PubMed: 30620402]
2. Willingham SB, Hotson AN, Miller RA. Targeting the A2AR in cancer; early lessons from the clinic. Curr Opin Pharmacol 2020;53:126–33 doi 10.1016/j.coph.2020.08.003. [PubMed: 33002857]
3. Hanna N, Johnson D, Temin S, Baker S Jr, Brahmer J, Ellis PM, et al. Systemic Therapy for Stage IV Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. J Clin Oncol 2017;35(30):3484–515 doi 10.1200/jco.2017.74.6065. [PubMed: 28806116]
4. Planchard D, Popat S, Kerr K, Novello S, Smit EF, Faivre-Finn C, et al. Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2019;30(5):863–70 doi 10.1093/annonc/mdy474. [PubMed: 31987360]
5. Mediavilla-Varela M, Luddy K, Noyes D, Khalil FK, Neuger AM, Soliman H, et al. Antagonism of adenosine A2A receptor expressed by lung adenocarcinoma tumor cells and cancer associated fibroblasts inhibits their growth. Cancer Biol Ther 2013;14(9):860–8 doi 10.4161/cbt.25643. [PubMed: 23917542]
6. Whiteside TL. Targeting adenosine in cancer immunotherapy: a review of recent progress. Expert Rev Anticancer Ther 2017;17(6):527–35 doi 10.1080/14737140.2017.1316197. [PubMed: 28399672]
7. Fishman P, Bar-Yehuda S, Synowitz M, Powell JD, Klotz KN, Gessi S, et al. Adenosine receptors and cancer. Handb Exp Pharmacol 2009(193):399–441 doi 10.1007/978-3-540-89615-9_14. [PubMed: 19639290]
8. Mediavilla-Varela M, Castro J, Chiappori A, Noyes D, Hernandez DC, Allard B, et al. A Novel Antagonist of the Immune Checkpoint Protein Adenosine A2a Receptor Restores Tumor-Infiltrating Lymphocyte Activity in the Context of the Tumor Microenvironment. Neoplasia (New York, NY) 2017;19(7):530–6 doi 10.1016/j.neo.2017.02.004.
9. Leone RD, Lo YC, Powell JD. A2aR antagonists: Next generation checkpoint blockade for cancer immunotherapy. Comput Struct Biotechnol J 2015;13:265–72 doi 10.1016/j.csbj.2015.03.008. [PubMed: 25941561]
10. Naing A, Gelderblom H, Gainor JF, Forde PM, Butler M, Lin CC, et al. A first-in-human phase I study of the anti-PD-1 antibody PDR001 in patients with advanced solid tumors. J Clin Oncol 2016;34:3060.
11. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45(2):228–47 doi 10.1016/j.ejca.2008.10.026. [PubMed: 19097774]

12. Gray JE, Saltos A, Tanvetyanon T, Haura EB, Creelan B, Antonia SJ, et al. Phase I/Ib Study of Pembrolizumab Plus Vorinostat in Advanced/Metastatic Non-Small Cell Lung Cancer. Clin Cancer Res 2019;25(22):6623–32 doi 10.1158/1078-0432.CCR-19-1305. [PubMed: 31409616]

13. Fong L, Hotson A, Powderly JD, Sznol M, Heist RS, Choueiri TK, et al. Adenosine 2A Receptor Blockade as an Immunotherapy for Treatment-Refractory Renal Cell Cancer. Cancer Discov 2020;10(1):40–53 doi 10.1158/2159-8290.Cd-19-0980. [PubMed: 31732494]

14. Fong L, Hotson A, Powderly JD, Sznol M, Heist RS, Choueiri TK, et al. Adenosine 2A Receptor Blockade as an Immunotherapy for Treatment-Refractory Renal Cell Cancer. Cancer discovery 2020;10(1):40–53 doi 10.1158/2159-8290.Cd-19-0980. [PubMed: 31732494]

15. Lin C-C, Joerger M, Grell P, Chiappori AA, Leal TA, Kasper S, et al. Continuous vs intermittent adenosine 2A receptor (A2AR) inhibition in preclinical colon cancer (CC) models and in a Phase (Ph) II study of taminadenant (NIR178) + spartalizumab (PDR001) in patients (pts) with non-small cell lung cancer (NSCLC). Eur J Cancer 2020;138:24.

16. Bendell J, Bauer T, Patel M, Falchook G, Karlix JL, Lim E, et al. Abstract CT026: Evidence of immune activation in the first-in-human Phase Ia dose escalation study of the adenosine 2a receptor antagonist, AZD4635, in patients with advanced solid tumors. Cancer research 2019;79(13 Supplement):CT026–CT doi 10.1158/1538-7445.Am2019-ct026.

17. Young A, Ngiow SF, Barkauskas DS, Sult E, Hay C, Blake SJ, et al. Co-inhibition of CD73 and A2AR Adenosine Signaling Improves Anti-tumor Immune Responses. Cancer cell 2016;30(3):391–403 doi 10.1016/j.ccell.2016.06.025. [PubMed: 27622332]

18. Streicher K, Higgs BW, Wu S, Coffman K, Damera G, Durham N, et al. Increased CD73 and reduced IFNG signature expression in relation to response rates to anti-PD-1(L1) therapies in EGFR-mutant NSCLC. Journal of Clinical Oncology 2017;35(15_suppl):11505- doi 10.1200/JCO.2017.35.15_suppl.11505.

19. Passarelli A, Aieta M, Sgambato A, Gridelli C. Targeting Immunometabolism Mediated by CD73 Pathway in EGFR-Mutated Non-small Cell Lung Cancer: A New Hope for Overcoming Immune Resistance. Frontiers in immunology 2020;11:1479- doi 10.3389/fimmu.2020.01479. [PubMed: 32760402]

20. ClinicalTrials.gov. A Phase I/Ib Study of NZV930 Alone and in Combination With PDR001 and /or NIR178 in Patients With Advanced Malignancies. Available at: https://clinicaltrials.gov/ct2/show/NCT03549000. Accessed: August 25, 2020.

21. ClinicalTrials.gov. KAZ954 Alone and With PDR001, NZV930 and NIR178 in Advanced Solid Tumors. Available at: https://clinicaltrials.gov/ct2/show/NCT04237649. Accessed: August 25, 2020.

Translational Relevance

Taminadenant is a potent and selective adenosine 2A receptor (A2AR) antagonist that binds to the receptor and inhibits accumulation of cyclic adenosine monophosphate. This article describes the results of a first-in-human, phase I/Ib study of taminadenant as both a single agent and in combination with spartalizumab in patients with advanced non-small cell lung cancer. Taminadenant was well tolerated both with and without spartalizumab combination, with only 20.0% and 12.0% patients discontinuing due to adverse events in the respective groups. The safety profile was consistent with that of another A2AR antagonist, ciforadenant, used in combination with the programmed cell death ligand-1 (PD-L1) inhibitor, atezolizumab, for renal cell cancer. The maximum tolerated dose was determined and taminadenant is currently being explored in several clinical trials in combination with spartalizumab, NZV930 (an anti-CD73 monoclonal antibody), or KAZ954 (an anti-ectonucleoside triphosphate disphosphohydrolase monoclonal antibody) for patients with advanced malignancies.

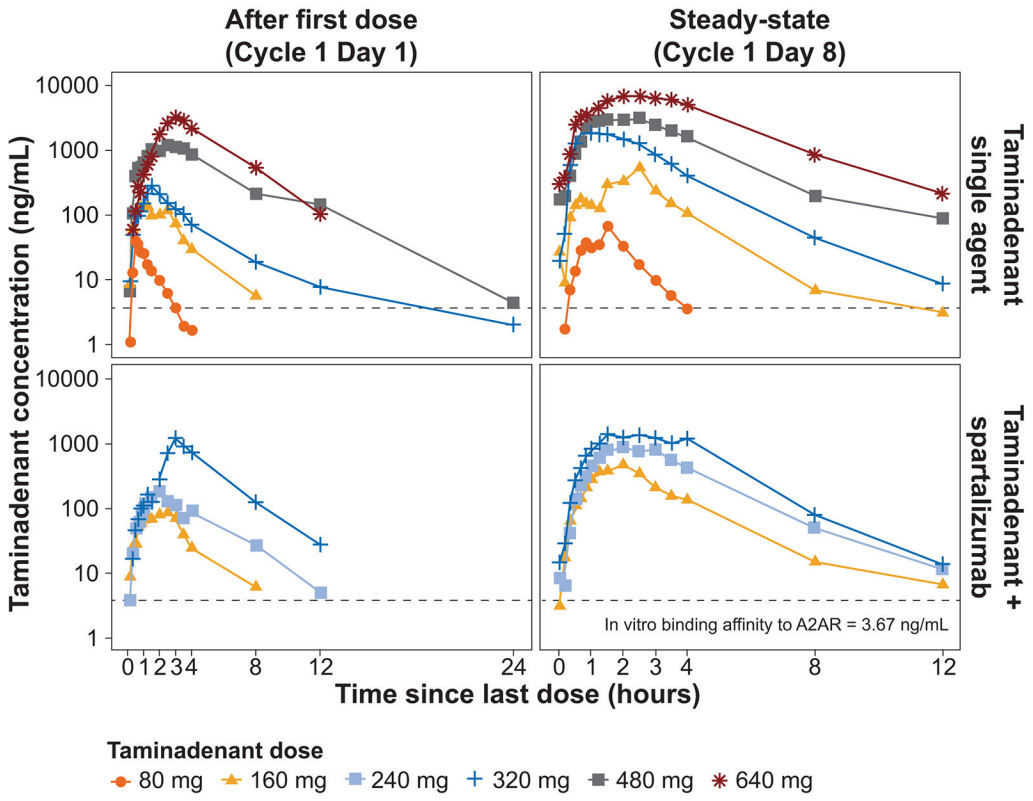

Figure 1. Geometric mean plasma concentration–time profiles of taminadenant, by visit and treatment group.

Data cut-off: January 15, 2020. Abbreviations: A2AR, adenosine 2A receptor.

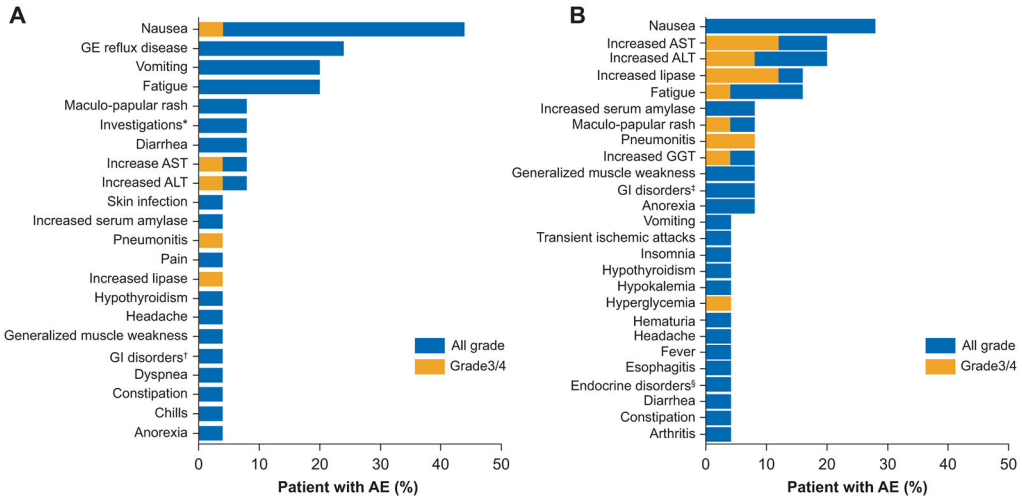

Figure 2. Tornado plot of adverse events, thought to be related to study treatment, reported in patients treated with taminadenant single agent

(A) and taminadenant in combination with spartalizumab (B). *Visual changes, shakiness; †Occasional indigestion; ‡Hypomotility of the gastrointestinal tract and intermittent gastrointestinal upset; §Elevated thyroid-stimulating hormone. Data cut-off: January 15, 2020. Abbreviation: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GE, gastro-esophageal; GGT, gamma-glutamyltransferase; GI, gastrointestinal.

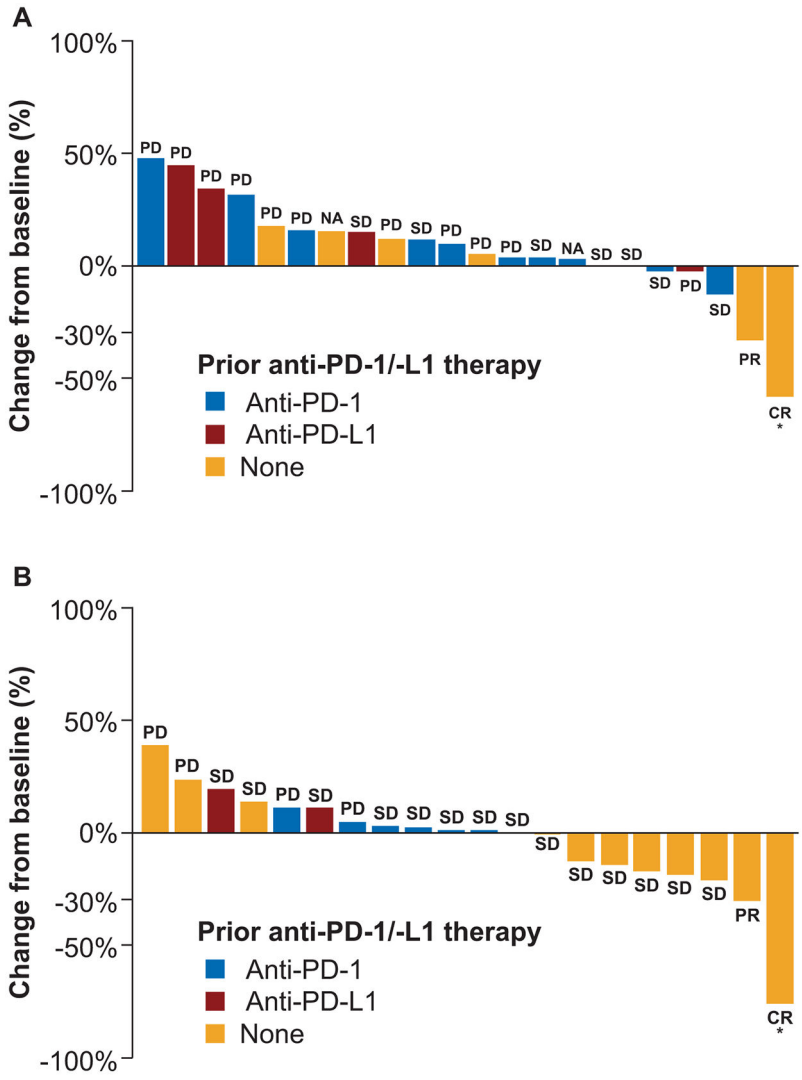

Figure 3. Best percentage change from baseline according to prior anti-PD-1/PD-L1 therapy in patients treated with taminadenant single agent

(A) and taminadenant in combination with spartalizumab (B). *CR does not revert to a 100% reduction in tumor size as the baseline target lesions were lymph nodes considered non-pathologic at best response; sizes decreased from 1.5 cm and 1.6 cm to 0.6 cm and 0.7 cm, respectively (any pathological lymph nodes are required to have a reduction in short axis to <10 mm to qualify for a CR). Data cut off: January 15, 2020. Abbreviations: CR, complete response; NA, not assessed; PD, progressive disease; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1; PR, partial response; SD, stable disease.

Table 1.

Patient baseline characteristics

Characteristic	Taminadenant single agent (n=25)	Taminadenant + spartalizumab (n=25)
Median age, years (range)	68 (49–89)	64 (49–85)
Sex, n (%)		
Female	13 (52.0)	10 (40.0)
Male	12 (48.0)	15 (60.0)
Race, n (%)		
Caucasian	25 (100)	24 (96.0)
Black or African American	0	1 (4.0)
Ethnicity, n (%)		
Non-Hispanic	25 (100)	24 (96.0)
Hispanic or Latino	0	1 (4.0)
ECOG PS, n (%)		
0	3 (12)	6 (24)
1	21 (84)	19 (76)
2	1 (4)	0
Prior lines of therapy[a]		
Median (range)	2 (2–5)	2 (1–6)
Not available	13	0
Prior immunotherapy, n (%)	19 (76.0)	9 (36.0)
Anti-PD-1	13 (52.0)	7 (28.0)
Anti-PD-L1	6 (24.0)	2 (8.0) [d]
Not available[b]	6 (24.0) [c]	16 (64.0)
Smoking history, n (%)[e]		
Current smoker	2 (8.0)	2 (8.0)
Previous smoker	18 (72.0)	18 (72.0)
Never smoked	4 (16.0)	3 (12.0)
Histology, n (%)		
Adenocarcinoma, NOS	20 (80.0)	20 (80.0)
Non-small cell carcinoma	1 (4.0)	2 (8.0)
Squamous cell carcinoma	4 (16.0)	3 (12.0)
Mutation status, n[f]		
EGFR	1	2
ALK	0	0
Other	0	1
KRAS	8	4
Metex14	0	1
Other mutation/amplification	4	12

Characteristic	Taminadenant single agent (n=25)	Taminadenant + spartalizumab (n=25)
No mutations	6	12
Unknown (*EGFR*/*ALK* negative)	9	5

[a] Includes radiotherapy

[b] This refers to the absence of any evidence of the patient having received prior immunotherapy in the available medical records

[c] One patient in the taminadenant single-agent group received prior immunotherapy that was not classified as either anti-PD-1– or anti-PD-L1

[d] One patient in the taminadenant plus spartalizumab group had received both prior anti-PD-1 and anti-PD-L1–targeted therapy, anti-PD-L1 was the most recent prior to starting therapy

[e] Smoking history was unknown in one patient in the taminadenant single-agent group and two patients in the taminadenant plus spartalizumab group

[f] Patients with multiple mutations were counted more than once. Data cut-off: January 15, 2020.

Abbreviations: NOS, not otherwise specified; PD-1, programmed cell death-1; PD-L1, programmed cell death ligand-1.

Table 2.

Summary of clinical benefit

	Taminadenant single agent (n=25)	Taminadenant + spartalizumab (n=25)
Best overall response, n (%) [a]		
Complete response	1 (4.0)	1 (4.0)
Partial response	1 (4.0)	1 (4.0)
Stable disease	7 (28.0)	14 (56.0)
Progressive disease	12 (48.0)	8 (32.0)
Non-evaluable	4 (16.0)	1 (4.0)
Disease control rate [b,c] **, % (95% CI)**	42.9 (21.8–66.0)	66.7 (44.7–84.4)
Overall response rate [c,d] **, % (95% CI)**	9.5 (1.2–30.4)	8.3 (1.0–27.0)

[a] Investigator-assessed per Response Evaluation Criteria In Solid Tumor version 1.1

[b] Calculated based on the number of evaluable patients

[c] Disease control rate = complete response + partial response + stable disease

[d] Overall response rate = complete response + partial response. Data cut-off: January 15, 2020.

Abbreviation: CI, confidence interval.