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Original Research

Phase II trial of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors SWOG/NCI experience: invasive mucinous or non-mucinous lepidic adenocarcinoma of the lung (formerly bronchioloalveolar carcinoma)

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Abstract

Background: Anti-programmed death-1 (PD-1)/cytotoxic T lymphocyte antigen-4 antibodies are efficacious in various malignancies.

Objectives: This study presents the first results of ipilimumab–nivolumab in invasive mucinous or non-mucinous lepidic adenocarcinoma (invasive mucinous adenocarcinoma (IMA) or invasive non-mucinous lepidic adenocarcinomas (INLA), respectively) of the lung.

Design: Dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART) is a prospective, open-label, multicenter (1016 US sites), multi-cohort phase II trial of ipilimumab (1 mg/kg intravenously (IV) every 6 weeks) plus nivolumab (240 mg IV every 2 weeks).

Methods: Participants histologically diagnosed with advanced IMA or INLA, who had not responded to at least one line of therapy, were included in the bronchioloalveolar carcinoma cohort. The primary endpoint was the overall response rate (ORR) by Response Evaluation Criteria in Solid Tumors (confirmed complete and partial responses (CR and PR)). Secondary endpoints were progression-free survival (PFS), overall survival (OS), clinical benefit rate (CBR; stable disease (SD) $\geq$ 6 months plus ORR), and toxicity.

Results: Eight evaluable patients (median age: 77 years; the number of prior therapies ranged from 0 to 4; one patient with prior exposure to a PD-1 inhibitor; comprising six IMA and two INLA) were treated. One IMA had a 40% regression (PFS 45.2+ months, PD-L1 0%, KRAS G12C mutated, tumor mutational burden [TMB] 13 mut/Mb). One INLA had 66% regression (PFS 23.8 months, PD-L1 unknown, no actionable mutations, TMB 3 mut/Mb). Overall ORR was 25.0% (2/8) and CBR, 62.5% (5/8); PFS for the patients with SD $>$ 6 months was 43.4+, 11.7+, and 8.3 months. The median PFS was 16 months (5.3–not reached) and the median OS was 32.2 months (14.6–not reached). The toxicity profile was similar to previous reports.

Conclusion: Ipilimumab plus nivolumab in the bronchioloalveolar carcinoma cohort (IMA, INLA) resulted in a durable ORR of 25.0% and CBR of 62.5% (PFS, 8.3 11.7+. 23.8 (PR), 43.4+ and 45.2+ (PR) months). Correlative studies to determine response and resistance markers are ongoing. Expanded prospective studies are warranted.

Trial registration: ClinicalTrials.gov registry: NCT02834013.

Keywords: DART, invasive mucinous adenocarcinoma, ipilimumab, lepidic adenocarcinoma, nivolumab

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Introduction

Pure bronchioloalveolar carcinoma comprises less than 4% of all non-small-cell lung carcinomas (NSCLCs) and demonstrates a higher prevalence in women, never-smokers, and those of Asian descent.[1] Unlike other NSCLC subtypes, bronchioloalveolar carcinoma displays a distinctive radiographic appearance, including multifocal or diffuse ground-glass opacities, lepidic growth pattern, minimal extra-thoracic spread, and frequent intrathoracic recurrence.[2]

Major updates to the classification of lung adenocarcinomas were made in 2011 by the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS).[3] These were further revised in the 2015 and 2021 WHO Classification, leading to new categories for bronchioloalveolar carcinoma based on clinical, radiological, and pathological attributes.[4,5] There is an unmet clinical need in the case of the subtypes of invasive adenocarcinomas, specifically invasive mucinous adenocarcinoma (IMAs) and invasive non-mucinous lepidic adenocarcinomas (INLAs).

Since the recent updates, the prognosis for patients with advanced IMAs has not been clearly defined. A study involving 79 such patients, with 82.3% at stage III–IV, revealed a median survival of 20.1 months (95% confidence interval (CI) 14.7–25.6 months).[6] Regardless of stage, variations in IMA phenotypes may affect the prognosis, where acinar-predominant (5-year overall survival (OS) 50.0%) and pneumonic (5-year disease-free survival 0%) types fare worse.[7–9] Radiographically, IMAs with spontaneous regression of airspace opacities (SRA) ($n = 14$) tend to have larger ($p < 0.001$), multifocal ($p < 0.001$), pneumonic-type ($p < 0.001$) lesions, with advanced stages of disease ($p < 0.001$) and reduced survival ($p < 0.001$) (median progression-free survival (PFS)/OS 4.0/24.0 months in SRA; 24.0/106.3 months in non-SRA).[10]

Similar to IMAs, the clinical outcomes of individuals with INLA in advanced stages warrant more extensive research using larger datasets. Some insights might be gleaned from a phase II trial involving 133 patients with INLAs, with 91.0% classified as stage IIIB–IV.[11] They were evenly randomized to receive either erlotinib or combination therapy of carboplatin–paclitaxel, resulting in an overall median OS of 20.1 months. Other studies, exploring both early and advanced stages, reveal that patients exhibiting multifocal ground-glass/lepidic features can have a 5-year OS rate ranging from 64% to 100%.[12] Of those identified with a diffuse pneumonic type, 60% displayed bilateral aerogenous-restricted metastases, often leading to swift onset of acute respiratory distress and death before initiating cancer treatment.[13] In certain cases, the severity has led to the consideration of dual lung transplantation.[14]

As with other types of adenocarcinomas, surgery is the primary treatment option for IMAs and INLAs. For cases that are either inoperable or have metastasized, molecular profiling can be used to select appropriate systemic therapy.[15] However, managing advanced cases can be complicated by the lack of histological subtyping in many studies and the potential for chemoresistance.[16] As a result, innovative approaches, such as immune checkpoint inhibitors (ICIs), are worth exploring, given their potential in treating various types of tumors, including advanced NSCLC.[17]

The dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART) study investigated the use of dual checkpoint inhibition with anti-programmed death-1 (PD-1) and anti-cytotoxic T lymphocyte antigen-4 (CTLA-4) ICI in rare solid cancers, including IMA and INLA. SWOG S1609 DART trial is the first to report on the use of ipilimumab and nivolumab in the bronchioloalveolar carcinoma cohort (IMA, INLA).

Patients and methods

This trial was conducted at more than a thousand sites in the United States under the supervision of the Early Therapeutics and Rare Cancer Committee of the SWOG Cancer Research Network/National Cancer Institute (NCI). Nivolumab and ipilimumab agents used in the trial were provided by the Cancer Therapy Evaluation Program of the NCI through the NCI CRADA agreement with Bristol Myers Squibb (BMS). The manuscript was prepared in accordance with the SPIRIT-Outcomes 2022 Checklist.[18]

Rationale for included study population

In this basket trial, the list of rare and ultra-rare tumor histologies was derived from the RareCare

initiative, a European Commission project that established a consensus definition of rare tumors in collaboration with the NCI. This list includes tumor entities coded by ICD-O/WHO pathological classification with an incidence of less than 6 per 100,000 per year.[19] For this study, the RareCare list was refined to group tumors with similar histologies and exclude rare tumor types already being investigated for anti-CTLA-4 and anti-PD-1 therapies.

Inclusion criteria and patient selection

Patients eligible for the trial had a histologically confirmed diagnosis of advanced solid cancer and no treatment options known to extend OS, refused other treatments, or had contraindications to them. As the NCCN advocates that the optimal approach for managing any patient with cancer is participation in a clinical trial, this trial aligns with their recommendation. Patients needed to be at least 18 years old, have a Zubrod performance status ranging from 0 to 2, and exhibit adequate hematologic, hepatic, thyroid, adrenal axis, and renal function (absolute neutrophil count $\geqslant$1000/mcL, platelets $\geqslant$75,000/mcL, hemoglobin $\geqslant$8 g/dL, creatinine clearance $\geqslant$50 mL/min, total bilirubin $\leqslant$2.0 $\times$ institutional upper limit of normal (IULN), AST and ALT $\leqslant$3.0 $\times$ IULN, thyroid stimulating hormone (TSH) or free T4 serum $\leqslant$IULN, and normal adrenocorticotropic hormone (ACTH)). Adequate contraception was required during the study, and participants of childbearing potential had to provide a negative serum pregnancy test at the time of enrollment.

In cohort 12, participants were initially identified histologically using the outdated term "bronchioloalveolar carcinoma," in line with the terminology specified in the study protocol. They were later reclassified into various subtypes according to the 2021 IASLC/ATS/ERS lung adenocarcinoma classification guidelines.[3–5] Within these subtypes, individuals with IMA and INLA histologies were included in cohort 12. To maintain consistency and facilitate reference, the term "bronchioloalveolar carcinoma" was used throughout the duration of the trial to describe these newly defined subtypes. Assessment of tumor pathology and grading was carried out by pathologists from the participating institutions or by local pathologists. The study's principal investigators reviewed these pathology reports. No centralized pathology review was undertaken.

Treatment and monitoring

Patients received treatment consisting of nivolumab at a dose of 240 mg intravenously (IV) every 2 weeks and ipilimumab at a dose of 1 mg/kg IV every 6 weeks, administered continuously.[20] The protocol specified dose adjustments and temporary breaks from therapy to manage treatment-related toxicities. Patients were removed from protocol treatment if they experienced disease progression, symptomatic deterioration, treatment delays exceeding 56 days for any reason, unacceptable or immune-related toxicity with an inability to decrease prednisone dosage to less than 10 mg daily, or upon patient request.

At the start of each treatment cycle (or at least every 6 weeks), patients underwent various evaluations, including a medical history review, physical examination, laboratory analyses (such as complete blood count, comprehensive metabolic panel, TSH, free thyroxine, ACTH, cortisol, and lipase), and toxicity assessment. Dose modifications were made according to specific guidance criteria provided to manage immune-related adverse events. Disease burden was assessed using imaging studies conducted before the study, at week 8, week 16, week 24, and then every 12 weeks until disease progression.

Statistical methods and outcomes

The primary endpoint was the overall response rate (ORR; confirmed complete and partial responses (CR and PR, respectively)) by RECIST v1.1 criteria per investigator. The study was powered to differentiate between a null hypothesis of a 5% ORR versus an alternative hypothesis of a 30% ORR. A two-stage design was utilized; in the first stage, if at least one of the first six eligible patients who received protocol therapy had a confirmed CR or PR, an additional 10 patients were to be enrolled. Two or more patients with a confirmed CR or PR of 16 were considered evidence of activity (87% power, one-sided alpha = 13%).

Secondary objectives included PFS per RECISTv1.1, OS, clinical benefit rate (CBR; stable disease (SD) $\geqslant$6 months plus ORR), ORR per immune-related RECIST (iRECIST), PFS per iRECIST, and toxicity assessment. PFS was measured from the first day of protocol therapy to the time of disease progression or death from any cause. Patients who were last known to be alive

without disease progression were censored at the date of their last contact. OS was measured from the date of protocol registration to the date of death from any cause, with patients last known to be alive censored at the date of their last contact. PFS and OS were estimated using the Kaplan–Meier method, and medians were calculated using the Brookmeyer and Crowley method. Point estimate CIs, such as 6-month PFS, were calculated using the log–log transformation. All statistical analyses were executed with R version 4.3.3.

Results

Patient characteristics

Patients enrolled in the S1609 study from January 2017 through March 2023, with the longest individual patient follow-up period reaching 5 years. The bronchioloalveolar carcinoma cohort (IMA, INLA) enrolled eight patients registered from 6 of the 1016 participating National Clinical Trial Network institutions. All eight patients met the eligibility criteria, received treatment according to the protocol, and were included in the analyses (Table 1, Supplemental Table 1). Among them, six had advanced IMA, and two had INLA. The median age was 77 years (range, 56–80 years), and 62.5% of the patients were male. The number of prior therapies ranged from 0 to 4, with one patient with prior exposure to a PD-1 inhibitor.

Table 1. Demographics and RECIST best response summary of eight evaluable patients in the bronchioloalveolar carcinoma cohort (IMA, INLA) treated on the DART immunotherapy protocol (nivolumab plus ipilimumab).

Bronchioloalveolar carcinoma cohort (IMA, INLA) (*n* = 8)	***n* (%)**
Age (years) (median (range))	77 (56–80)
Sex	
Female	3 (37.5)
Male	5 (62.5)
Performance status	
0	5 (62.5)
1	2 (25.0)
2	1 (12.5)
Ethnicity	
Hispanic	0 (0.0)
Non-Hispanic	8 (100.0)
Race	
White	7 (87.5)
Black	1 (12.5)
Response	
Confirmed PR	2 (25.0)
SD ⩾ 6 months	3 (37.5)
Clinical benefit[a]	5 (62.5)
SD < 6 months	1 (12.5)
Progression	2 (25.0)

[a]Clinical benefit = SD ⩾ 6 months plus confirmed objective responses.
DART, dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors; IMA, invasive mucinous adenocarcinoma; INLA, invasive non-mucinous lepidic adenocarcinoma; PR, partial response; RECIST, response evaluation criteria in solid tumors; SD, stable disease.

Outcomes

Among the eight evaluable patients in the bronchioloalveolar carcinoma cohort (IMA, INLA), the ORR was 25.0% (2/8), and the CBR was 62.5% (5/8) (Table 1). The best response observed was a confirmed PR in two patients (Table 1, Figures 1 and 2). At the time of analysis, there were three ongoing responses (Figure 2). One patient with the IMA subtype (PD-L1 0%, KRAS G12C mutated, TMB 13 mut/Mb) had an ongoing regression of 40% after 45.2+ months, and another patient with the INLA subtype (PD-L1 unknown, no actionable mutations, TMB 3 mut/Mb) had a regression of 66% with a PFS of 23.8 months. In addition, two out of four patients with an SD had ongoing PFS of 43.4+ (IMA subtype, PD-L1 unknown, KRAS G12A mutated) and 11.7+ months (INLA subtype, PD-L1 unknown, no actionable mutations), respectively. Among the four out of eight patients who remain alive, the PFS ranged from 11.7 to 45.2+ months. Overall, the 6-month PFS was 62% (95% CI 37%–100%), the 12-month PFS was 50% (95% CI 25%–100%); and the median PFS was 16 months (95% CI 5.3 months–not reached) (Figure 3). There was no change in patients' responses or PFS

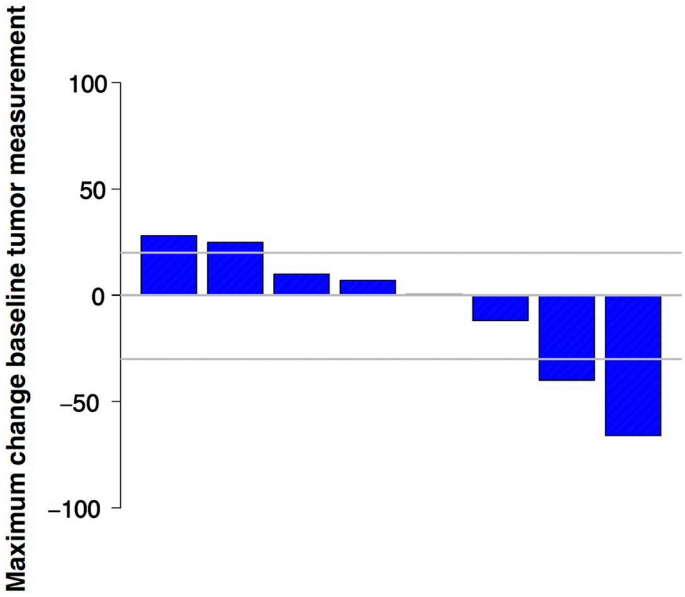

Figure 1. RECIST v1.1 waterfall plot indicating a maximum change in baseline tumor measurement following protocol therapy.
Bars below the line indicate regressing disease; above the line, enlarging disease.
RECIST, Response Evaluation Criteria in Solid Tumors.

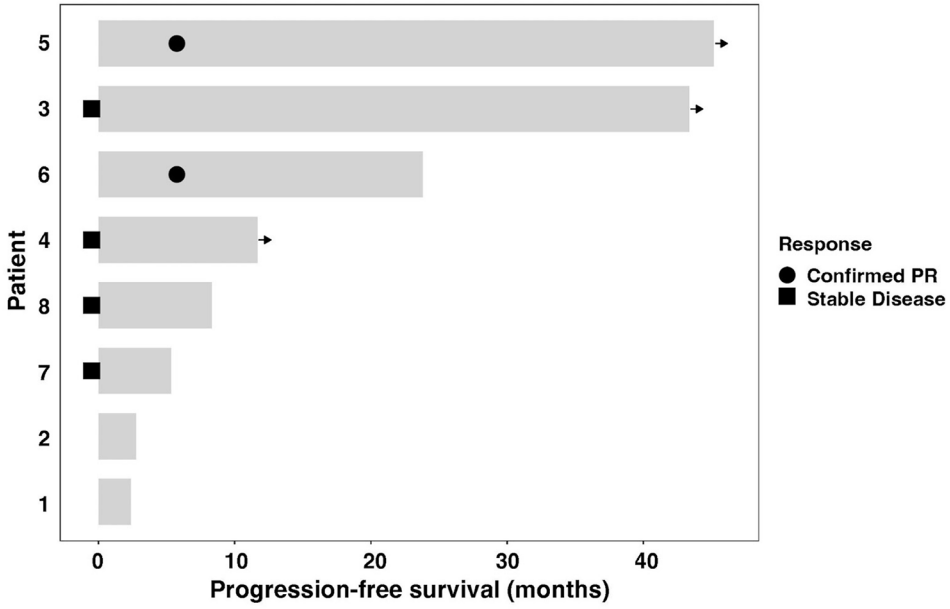

Figure 2. RECIST v1.1 Swimmer's plot of PFS following protocol therapy.
Bars indicate PFS per individual patient. Response patterns are specified with symbols as described.
PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

according to iRECIST criteria. The 6-month OS rate was 88% (95% CI 67%–100%), which was equal to the 12-month OS rate. The median OS was 32.2 months (95% CI 14.6 months–not reached) (Figure 3).

Toxicities

All patients in the bronchioloalveolar cohort (IMA, INLA) ($n=8$) experienced adverse events of any grade at least possibly drug-related, with 50.0% ($n=4$) experiencing grade 3–4 adverse

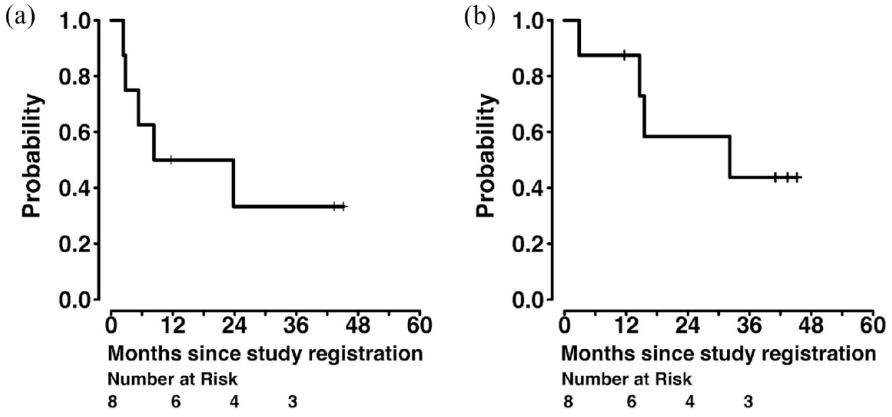

Figure 3. RECIST v1.1 (a) progression-free and (b) overall survival following protocol therapy.
RECIST, Response Evaluation Criteria in Solid Tumors.

events (namely, fatigue, delirium, type 1 diabetes, enterocolitis, flu-like symptoms, hypoxia, pancreatitis, respiratory failure, syncope, hypokalemia, hyponatremia, and elevation of serum lipase, amylase, glucose) (Table 2). The most common adverse events reported included fatigue (75.0%, $n=6$), maculopapular rash (50.0%, $n=4$), dry mouth (37.5%, $n=3$), creatinine elevation (37.5%, $n=3$), and hypoalbuminemia (37.5%, $n=3$). Two treatment-related adverse events led to treatment discontinuation, but no deaths were reported as a result of these adverse events. Overall, 62.5% ($n=5$) of adverse events were considered immune mediated, with the most common being maculopapular rash (50.0%, $n=4$), lipase elevation (25.0%, $n=2$), and serum amylase elevation (25.0%, $n=2$). Grade 3 or higher immune-mediated adverse events occurred in one case (12.5%).

Discussion

The DART trial is a phase II clinical trial that involves an open-label, multicenter, multi-cohort study investigating the efficacy of the ipilimumab plus nivolumab combination regimen. This paper focuses on the bronchioloalveolar carcinoma cohort (IMA, INLA). The regimen was overall tolerable in this cohort and induced a durable PR (45.2+ months in one IMA, 23.8 months in one INLA), with an overall ORR of 25.0% (2/8) and CBR, which includes ORR plus SD of at least 6 months, of 62.5% (5/8); the PFS rates of these five patients were 8.3, 11.7+, 23.8, 43.4+, and 45.2+ months.

Prior studies remain unclear as to whether or not ICI treatment is clinically beneficial for IMA or INLA. A retrospective study at a single center revealed that 18 out of 79 patients with progressive, recurrent, or metastatic IMAs who were administered immunotherapy (including nivolumab, pembrolizumab, atezolizumab, avelumab, and durvalumab) had a longer OS compared to those who received chemotherapy or targeted therapy (hazard ratio (HR) 0.28; $p=0.01$).[6] In addition, three cases of IMA without epidermal growth factor receptor (EGFR) mutations and $\leqslant$1% PD-L1 expression had a positive response to pembrolizumab, with two cases experiencing PR, but for only 1.25–1.5 months, and one case of SD with PFS exceeding 20 months.[21,22]

The unique tumor microenvironments (TME) of INLAs and IMAs may indicate differential responses to ICIs. In a study involving 31 patients with IMAs and 27 patients with non-IMA subtypes, patients with IMAs had significantly lower levels of PD-L1 expression and CD8+ tumor-infiltrating lymphocytes (TILs) infiltration compared to patients with non-IMA subtypes (9.7% (3/31) and 35.5% (11/31) in IMA, respectively; 48.1% (13/27) and 81.5% (22/27) in non-IMA, respectively; $p<0.001$), consistent with previous studies.[23–27] Among the 31 patients with IMAs in the same study, those with CD8+ TIL infiltration had a worse prognosis than those without (median OS 47.2 vs 60.2 months, $p=0.02$; HR = 5.60, $p=0.02$).[24] Finally, tumor mutational burden, a biomarker for immunotherapy response, was found to be low in IMAs in The

Table 2. Potential drug-related adverse events among eight evaluable patients in the bronchioloalveolar carcinoma cohort (IMA, INLA) treated on the DART immunotherapy protocol (nivolumab plus ipilimumab).

Bronchioloalveolar carcinoma cohort (IMA, INLA) (*n* = 8)	Any grade	Grade 3–4	Grade 5
Any	8 (100.0%)	4 (50.0%)	0 (0.0%)
Serious	3 (37.5%)	3 (37.5%)	0 (0.0%)
Led to discontinuation	2 (25.0%)	2 (25.0%)	0 (0.0%)
Lead to death	0 (0.0%)	0 (0.0%)	0 (0.0%)
>10% of patients			
Symptoms/conditions			
Fatigue	6 (75.0%)	1 (12.5%)	0 (0.0%)
Maculo-papular rash	4 (50.0%)	0 (0.0%)	0 (0.0%)
Dry mouth	3 (37.5%)	0 (0.0%)	0 (0.0%)
Vomiting	3 (37.5%)	0 (0.0%)	0 (0.0%)
Anorexia	2 (25.0%)	0 (0.0%)	0 (0.0%)
Constipation	2 (25.0%)	0 (0.0%)	0 (0.0%)
Diarrhea	2 (25.0%)	0 (0.0%)	0 (0.0%)
Limb edema	2 (25.0%)	0 (0.0%)	0 (0.0%)
Hypothyroidism	2 (25.0%)	0 (0.0%)	0 (0.0%)
Nausea	2 (25.0%)	0 (0.0%)	0 (0.0%)
Delirium	1 (12.5%)	1 (12.5%)	0 (0.0%)
Diabetes type 1	1 (12.5%)	1 (12.5%)	0 (0.0%)
Enterocolitis	1 (12.5%)	1 (12.5%)	0 (0.0%)
Flu like symptoms	1 (12.5%)	1 (12.5%)	0 (0.0%)
Hypoxia	1 (12.5%)	1 (12.5%)	0 (0.0%)
Pancreatitis	1 (12.5%)	1 (12.5%)	0 (0.0%)
Respiratory failure	1 (12.5%)	1 (12.5%)	0 (0.0%)
Syncope	1 (12.5%)	1 (12.5%)	0 (0.0%)
Abdominal pain	1 (12.5%)	0 (0.0%)	0 (0.0%)
Acute kidney injury	1 (12.5%)	0 (0.0%)	0 (0.0%)
Adrenal insufficiency	1 (12.5%)	0 (0.0%)	0 (0.0%)
Agitation	1 (12.5%)	0 (0.0%)	0 (0.0%)
Allergic reaction	1 (12.5%)	0 (0.0%)	0 (0.0%)
Arthralgia	1 (12.5%)	0 (0.0%)	0 (0.0%)
Cough	1 (12.5%)	0 (0.0%)	0 (0.0%)

(Continued)

Table 2. (Contined)

Bronchioloalveolar carcinoma cohort (IMA, INLA) (*n* = 8)	Any grade	Grade 3–4	Grade 5
Dermatitis radiation	1 (12.5%)	0 (0.0%)	0 (0.0%)
Dyspnea	1 (12.5%)	0 (0.0%)	0 (0.0%)
Gastroesophageal reflux disease	1 (12.5%)	0 (0.0%)	0 (0.0%)
Gum sensitivity	1 (12.5%)	0 (0.0%)	0 (0.0%)
Headache	1 (12.5%)	0 (0.0%)	0 (0.0%)
Hematuria	1 (12.5%)	0 (0.0%)	0 (0.0%)
Hyperthyroidism	1 (12.5%)	0 (0.0%)	0 (0.0%)
Shingles	1 (12.5%)	0 (0.0%)	0 (0.0%)
Lip infection	1 (12.5%)	0 (0.0%)	0 (0.0%)
Localized edema	1 (12.5%)	0 (0.0%)	0 (0.0%)
Nasal congestion	1 (12.5%)	0 (0.0%)	0 (0.0%)
Neuralgia	1 (12.5%)	0 (0.0%)	0 (0.0%)
Extremity pain	1 (12.5%)	0 (0.0%)	0 (0.0%)
Papulopustular rash	1 (12.5%)	0 (0.0%)	0 (0.0%)
Pneumonitis	1 (12.5%)	0 (0.0%)	0 (0.0%)
Proteinuria	1 (12.5%)	0 (0.0%)	0 (0.0%)
Pruritus	1 (12.5%)	0 (0.0%)	0 (0.0%)
Growth of right supraclavicular area	1 (12.5%)	0 (0.0%)	0 (0.0%)
Skin infection	1 (12.5%)	0 (0.0%)	0 (0.0%)
Urinary tract infection	1 (12.5%)	0 (0.0%)	0 (0.0%)
Weight loss	1 (12.5%)	0 (0.0%)	0 (0.0%)
Laboratory abnormalities			
Creatinine increased	3 (37.5%)	0 (0.0%)	0 (0.0%)
Hypoalbuminemia	3 (37.5%)	0 (0.0%)	0 (0.0%)
Lipase increased	2 (25.0%)	1 (12.5%)	0 (0.0%)
Serum amylase increased	2 (25.0%)	1 (12.5%)	0 (0.0%)
Hyperglycemia	1 (12.5%)	1 (12.5%)	0 (0.0%)
Hypocalcemia	1 (12.5%)	0 (0.0%)	0 (0.0%)
Hypokalemia	1 (12.5%)	1 (12.5%)	0 (0.0%)
Hyponatremia	1 (12.5%)	1 (12.5%)	0 (0.0%)

(Continued)

Table 2. (Contined)

Bronchioloalveolar carcinoma cohort (IMA, INLA) (*n* = 8)	Any grade	Grade 3–4	Grade 5
Alanine aminotransferase increased	1 (12.5%)	0 (0.0%)	0 (0.0%)
Aspartate aminotransferase increased	1 (12.5%)	0 (0.0%)	0 (0.0%)
Low hematocrit	1 (12.5%)	0 (0.0%)	0 (0.0%)
Low total protein	1 (12.5%)	0 (0.0%)	0 (0.0%)
RBC decreased	1 (12.5%)	0 (0.0%)	0 (0.0%)
T3 decreased	1 (12.5%)	0 (0.0%)	0 (0.0%)
Trace leukocyte esterase	1 (12.5%)	0 (0.0%)	0 (0.0%)
Low MPV	1 (12.5%)	0 (0.0%)	0 (0.0%)
Blood bilirubin increased	1 (12.5%)	0 (0.0%)	0 (0.0%)
Hemoglobin increased	1 (12.5%)	0 (0.0%)	0 (0.0%)
Lymphocyte count decreased	1 (12.5%)	0 (0.0%)	0 (0.0%)
White blood cells decreased	1 (12.5%)	0 (0.0%)	0 (0.0%)
Immune-mediated	5 (62.5%)	1 (12.5%)	0 (0.0%)
Maculo-papular rash	4 (50.0%)	0 (0.0%)	0 (0.0%)
Lipase increased	2 (25.0%)	1 (12.5%)	0 (0.0%)
Serum amylase increased	2 (25.0%)	1 (12.5%)	0 (0.0%)
Diarrhea	2 (25.0%)	0 (0.0%)	0 (0.0%)
Hypothyroidism	2 (25.0%)	0 (0.0%)	0 (0.0%)
Hyperthyroidism	1 (12.5%)	0 (0.0%)	0 (0.0%)
Pancreatitis	1 (12.5%)	1 (12.5%)	0 (0.0%)
Pneumonitis	1 (12.5%)	0 (0.0%)	0 (0.0%)
Pruritus	1 (12.5%)	0 (0.0%)	0 (0.0%)
Adrenal insufficiency	1 (12.5%)	0 (0.0%)	0 (0.0%)
Alanine aminotransferase increased	1 (12.5%)	0 (0.0%)	0 (0.0%)
Arthralgia	1 (12.5%)	0 (0.0%)	0 (0.0%)
Aspartate aminotransferase increased	1 (12.5%)	0 (0.0%)	0 (0.0%)
Blood bilirubin increased	1 (12.5%)	0 (0.0%)	0 (0.0%)

DART, dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors; IMA, invasive mucinous adenocarcinoma; INLA, invasive non-mucinous lepidic adenocarcinoma; MPV, mean platelet volume.

Cancer Genome Atlas exome dataset ($p = 0.01$), regardless of smoking history.[28,29] There is inconsistent information regarding PD-L1 expression levels in non-IMA subtypes. One study reported the highest PD-L1-positive areas (72.7%) in INLA ($n = 16$) among different growth patterns, such as solid ($n = 55$), acinar ($n = 73$), papillary ($n = 16$), or micropapillary ($n = 17$), with PD-L1 expression being a biomarker for immunotherapy response in patients with cancers, albeit an imperfect one.[30,31] However, another study found that most INLA tumors (10/15) expressed less than 1% PD-L1 expression.[25] More research is needed to establish a potential association between the response of different bronchioloalveolar carcinoma subtypes to ICIs and their unique TME.

Different molecular characteristics are observed in the mucinous and non-mucinous types. KRAS mutations are commonly found in IMA (63%–90% in IMA; 4%–15.6% in non-IMA; $p < 0.001$), while non-IMA is typically associated with EGFR mutations (0%–5% in IMA; 32.3%–56% in non-IMA; $p < 0.001$).[15,28,32–39] In a SWOG trial of 81 patients with bronchioloalveolar carcinoma subtypes treated with gefitinib, patients with EGFR/fluorescence in situ hybridization (FISH)-positive tumors had longer survival ($n = 26$; median PFS 9 months; median OS 18+ months) than patients with EGFR/FISH-negative tumors ($n = 55$; median PFS 4 months, HR = 1.67, $p = 0.07$; median OS 8 months, HR = 2.01, $p = 0.04$); in addition, 63% (12/19) of FISH-positive tumors demonstrated disease control compared to 39% (14/36) FISH-negative tumors.[40] Erlotinib was also effective in the bronchioloalveolar carcinoma subtype tumors harboring EGFR exon 19 or 21 mutation ($n = 18$; ORR 83%; median PFS 13 months; median OS 23 months) versus tumors with no demonstrable mutation ($n = 63$; ORR 7%, $p < 0.01$; median PFS 2 months, $p < 0.01$; median OS 17 months, $p = 0.65$).[41] NRG1 fusions, which are less common in IMAs (7%–27%), are linked to aggressive traits, such as inferior recurrence-free survival ($p < 0.001$), compared to KRAS-mutant IMAs.[32] Responses have been reported with afatinib (10-month PR as the best response) and the HER3-targeting antibody lumretuzumab (4-month SD as the best response) in NRG1 fusion-positive IMAs in the form of case reports.[42–45]

Overall, the DART trial, supported by the NCI, SWOG, and patient advocacy groups and investigating dual anti-PD-1 and anti-CTLA-4 blockade across 52 rare and ultra-rare tumor types, opened at 1016 sites across the United States and accrued nearly 800 patients in the past 5 years; this trial disproved the notion that rare tumor clinical trials are not feasible and served an unmet need with rare tumors. Thus far, the DART study has identified activity in a number of rare and ultra-rare tumors, including angiosarcoma, neuroendocrine tumors, metaplastic breast cancer, gestational trophoblastic neoplasia, and gallbladder cancer.[46–51] Weaknesses include the non-randomized nature, small sample size, heterogeneous patient population, lack of mandated central pathology review and radiology review, and lack of patients' biomarker data for subgroup analysis.

Conclusion

In conclusion, the combination of ipilimumab and nivolumab in the bronchioloalveolar carcinoma cohort (IMA, INLA) yielded an ORR of 25.0% and a CBR of 62.5% (PFS of 8.3, 11.7+, 23.8 (PR), 43.4+, and 45.2+ (PR) months). The responses were durable, with PRs lasting 45.2+ and 23.8 months in one IMA and one INLA, respectively. Correlative studies to identify response and resistance markers are ongoing. These results suggest the hypothesis that combinatorial immunotherapy may be beneficial in IMA and INLA, warranting validation with larger prospective clinical trials.

Declarations

Ethics approval and consent to participate

Ethics considerations: The original protocol and any modifications underwent thorough review and approval by SWOG, the NCI Central Institutional Review Board (CIRB), as well as the regulatory committees of participating institutions. Consent for participation: Each participant in the study provided their informed consent in writing, voluntarily, and the consent document was approved by the human subject protection committee of each participating institution.

Consent for publication

Not applicable.

Author contributions

Young Kwang Chae: Conceptualization; Funding acquisition; Investigation; Methodology; Resources; Supervision; Writing – original draft; Writing – review & editing.

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Competing interests

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Availability of data and materials

The data generated in this study are available upon request from the following instructions according

to SWOG policies: https://www.swog.org/sites/default/files/docs/2019-12/Policy43_0.pdf

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Supplemental material
Supplemental material for this article is available online.

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