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Lung Cancer

A Randomized Phase II Study of Metformin plus Paclitaxel/Carboplatin/Bevacizumab in Patients with Chemotherapy-Naïve Advanced or Metastatic Nonsquamous Non-Small Cell Lung Cancer

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Non-small cell lung cancer • Chemotherapy • Metformin

Abstract

Background. In the absence of a targeted oncogenic driver mutation or high programmed death-ligand 1 expression, systemic therapy with platinum-based doublet chemotherapy with or without bevacizumab has been the standard treatment in advanced or metastatic non-small cell lung cancer (NSCLC). Metformin has been shown to have antitumor effects via a variety of insulin-dependent and insulin-independent mechanisms and to be potentially synergistic with chemotherapy.

Materials and Methods. This open-label single-center phase II study (NCT01578551) enrolled patients with chemotherapy-naïve advanced or metastatic nonsquamous NSCLC and randomized them (3:1) to receive carboplatin, paclitaxel, and bevacizumab with (Arm A) or without (Arm B) concurrent metformin for four to six cycles followed by maintenance therapy with bevacizumab ± metformin continued until disease progression, intolerable toxicity, or study withdrawal. The primary outcome was 1-year progression free survival (PFS). Secondary outcomes included overall survival, response to therapy, and toxicity.

Results. A total of 25 patients were enrolled from August 2012 to April 2015, of whom 24 received at least one cycle of therapy administration. The study was stopped early due to slow accrual and changes in standard first-line therapy of advanced NSCLC. The 1-year PFS on Arm A ($n = 18$) was 47% (95% confidence interval [CI]: 25%–88%), which exceeded the historical control 1-year PFS of 15%. Median overall survival of patients treated on Arm A was 15.9 months (95% CI: 8.4–not available [NA]) and 13.9 months (95% CI: 12.7–NA) on Arm B. There were no significant differences in toxicity between the study arms.

Conclusion. To the authors' knowledge, this is the first study to show a significant benefit in PFS with the use of metformin in this patient population and is a signal of efficacy for metformin in advanced NSCLC. ***The Oncologist*** 2018;23:859–865

Implications for Practice: The anticancer effects of metformin continue to be elucidated. To the authors' knowledge, this is the first trial in nondiabetic advanced non-small cell lung cancer patients to show a significant change in outcome with the addition of metformin to standard first-line chemotherapy. Well tolerated and widely available, metformin is a drug that should be considered for further study in the lung cancer treatment landscape.

Introduction

In the absence of a targeted oncogenic driver mutation or high programmed death-ligand 1 expression, systemic therapy with platinum-based doublet chemotherapy with or without bevacizumab has long been the standard of care in advanced or metastatic (stage IIIB–IV) non-small cell lung cancer (NSCLC). Regardless of initial systemic treatment with chemotherapy, immune checkpoint inhibition, or targeted therapy, advanced or metastatic disease is incurable with current therapies [1, 2].

First-line chemotherapy for advanced or metastatic nonsquamous NSCLC includes four to six cycles of platinum-based doublet chemotherapy with or without bevacizumab, followed by maintenance therapy until disease progression [3]. The use of bevacizumab in this setting is supported by data from Eastern Cooperative Oncology Group (ECOG) 4599, the phase III trial showing that treatment with carboplatin and paclitaxel plus bevacizumab (compared with chemotherapy alone) resulted in

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a higher response rate (35% vs. 15%) and improved overall survival (12.3 vs. 10.3 months) that included a 1-year progression-free survival (PFS) of 15%. These increased response rates and improved survival rates led to its U.S. Food and Drug Administration approval in the first-line setting [4].

Metformin, a biguanide that is commonly prescribed and well tolerated in the treatment of type 2 diabetes, has been investigated for potential anticancer effects after epidemiologic studies found lower incidence of cancers among diabetic patients treated with metformin, compared with those diabetics managed by sulfonylureas or insulin [5–7]. In a retrospective study of breast cancer patients undergoing chemotherapy, a high frequency of complete pathological responses was noted in diabetic patients treated with metformin in addition to chemotherapy compared with diabetic patients receiving other diabetic treatment while undergoing chemotherapy [8]. Similar retrospective analysis of Surveillance, Epidemiology, and End Results data, metformin was found to significantly improve survival (hazard ratio 0.80, 95% confidence interval [CI]: 0.71–0.89) in metastatic NSCLC patients with diabetes even after adjusting for demographics, diabetes severity and treatment, cancer characteristics, and oncologic treatment [9]. In a second retrospective study of diabetic patients on metformin therapy with locally advanced NSCLC who received concurrent chemoradiotherapy, median PFS (41 vs. 15 months) and 2-year distant metastasis-free survival (74% vs. 53%) was significantly improved, although no difference in overall survival (OS) was found [10]. Collectively, these retrospective studies suggest that metformin has anticancer effects and that tight glucose control alone is not the only, or even primary, mechanism by which metformin exerts these effects.

Metformin alters cellular energy metabolism and is known to decrease hepatic gluconeogenesis in diabetes via adenosine monophosphate kinase (AMPK) dependent and independent mechanisms [11, 12]. Numerous investigations are ongoing to understand mechanisms of anticancer activities of metformin, and it is still controversial whether this activity is due to changes in the host metabolic environment—such as decreases in insulin-dependent stimulation of tumor growth—or a result of direct action on tumor cells [13–15]. For example, proposed mechanisms include decreasing insulin and insulin-like growth factor 1 (IGF-1) levels and decreasing insulin growth factor 1 receptor (IGF-1R) and insulin receptor (IR) levels [15]. Alternatively, likely direct cellular effects of metformin on cancer cells involve disruption of glycolysis and the electron transport chain in the tricarboxylic acid cycle, leading to generation of reactive oxygen species, decreased ATP production and NAD+/NADH ratios, and depletion of cellular aspartate, which is crucial for synthesis of nucleotides [16–19].

Although retrospective clinical data and laboratory studies both point to metformin having a potential role in cancer treatment, efficacy of this drug in cancer therapy has not been convincingly validated in prospective trials. In particular, limited data evaluating the effects of metformin in lung cancer have been available. Responding to this need, our prospective phase II clinical trial evaluates response rate and PFS of platinum-based doublet chemotherapy ± metformin in chemotherapy-naïve advanced or metastatic nonsquamous NSCLC.

Materials and Methods

Patient Population

Eligible candidates for this study (NCT01578551) had measurable histologically or cytologically confirmed chemotherapy-naïve stage IIIB or IV nonsquamous NSCLC. Patients with known epidermal growth factor receptor (*EGFR*) mutation were allowed to receive prior oral EGFR tyrosine kinase inhibitor therapy. Eligible patients were 18 years of age or older, had an ECOG performance status score of 0 or 1, a life expectancy of $\geq$12 weeks, and normal organ and bone marrow function. Patients with treated, stable brain metastases were eligible. Key exclusion criteria were a history of or current diagnosis of diabetes mellitus, uncontrolled hypertension (defined as $>$150/$>$100), a history of gross hemoptysis, a history of thrombotic or hemorrhagic disorders, therapeutic anticoagulation or chronic daily aspirin ($>$325 mg per day), prior use of chemotherapy, or human immunodeficiency virus positivity on combination antiretroviral therapy. The complete eligibility criteria are provided in the study protocol, available in supplemental online data. This study was conducted according to U.S. and international standards of Good Clinical Practice, with approval from the Johns Hopkins Medicine Institutional Review Board. All patients provided written informed consent prior to study protocol therapy initiation.

Study Design

This open-label phase II study assessed the addition of metformin to standard chemotherapy in patients with chemotherapy-naïve advanced or metastatic nonsquamous NSCLC (Fig. 1). The study was designed to treat a total of 60 patients; 45 patients with standard chemotherapy plus metformin, and 15 patients with chemotherapy alone. This sample size was determined to provide around 84% power to detect an increase in the 1-year PFS to 30% (from a null 1-year PFS of 15%) in the overall lung cancer population, based on the lower 95% confidence bound exceeding 15%. The calculation assumed an accrual rate of three patients every 2 months and minimum follow-up of 12 months. The 15% null 1-year PFS value was based on historical data [4] and might not apply to our study population. We therefore included a concurrent control group to allow assessment of the assumed historical benchmark. The study randomized patients 3:1 to standard chemotherapy with metformin or without metformin, respectively. On both arms, patients received standard dose carboplatin (area under curve = 6 mg/ml/minute), paclitaxel (200 mg/m^2), and bevacizumab (15 mg/kg) for four to six 21-day cycles followed by bevacizumab (15 mg/kg) maintenance every 21 days. Patients randomized to the intervention arm (Arm A) were to receive metformin (1,000 mg twice a day) with their chemotherapy; patients on the control arm, Arm B, received chemotherapy alone. Patients remained on maintenance therapy indefinitely, until disease progression, intolerable toxicity, or patient study withdrawal.

The primary statistical analysis of 1-year PFS compared the lower 95% confidence bound of the estimated 1-year PFS to 15%. Secondary endpoints of safety, response rates, and overall survival were to be compared with previously published studies of the carboplatin, paclitaxel, and bevacizumab regimen in chemotherapy-naïve advanced nonsquamous NSCLC using

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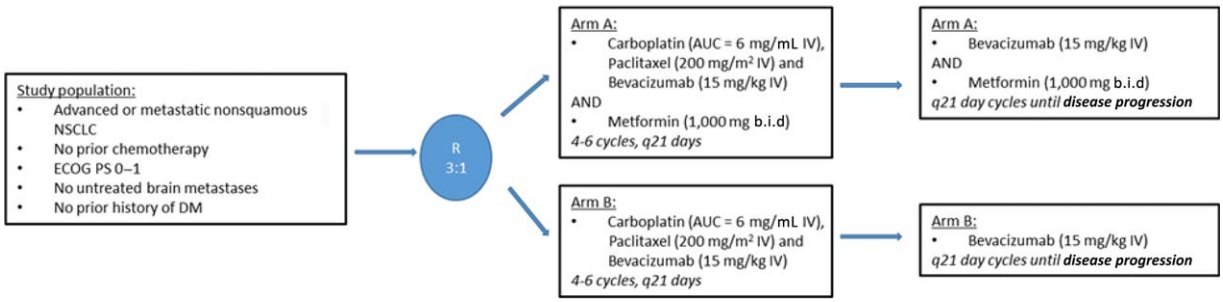

Figure 1. Study schema.
Abbreviations: DM, diabetes mellitus; ECOG PS, Eastern Cooperative Oncology Group performance score; IV, intravenously; NSCLC, non-small cell lung cancer; q21 days, every 21 days.

Table 1. Demographic characteristics by arm

Characteristic	Arm A, $n = 19$, *n* (%)	Arm B, $n = 6$, *n* (%)
Age in years, median (range)	58 (37–74)	64 (55–70)
Gender		
Male	7 (37)	2 (33)
Female	12 (63)	4 (67)
Caucasian	16 (84)	6 (100)
Smoker	13 (68)	5 (83)
ECOG PS		
0	0 (0)	0 (0)
1	19 (100)	6 (100)
Driver mutations		
Present (*EGFR/ALK*)	3 (16)	1 (17)
Not present[a]	10 (53)	3 (50)
Not tested/insufficient tissue	6 (31)	2 (33)

[a]Six patients on Arm A, three patients on Arm B with *KRAS* mutations.
Abbreviations: ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance score; EGFR, epidermal growth factor receptor.

historical control rates of 35% for response rate and 1-year survival of 51% [4].

Assessments

Safety

Safety assessments included history and physical examinations, ECOG performance status assessments, adverse event assessment via the Common Terminology Criteria for Adverse Events (CTCAE) v4.0, comprehensive chemistry panel, coagulation studies, lactate dehydrogenase, complete blood counts with differential, and urinalysis. Safety assessments were performed at screening and at least once during each therapy cycle, on day 1. Adverse event severity was graded according to the National Cancer Institute CTCAE, version 4.0. All adverse effects of grade 3 or higher were tabulated, regardless of attribution to study drug. Adverse event relationship to therapy (definitely, probably, possibly, unlikely, or unrelated) were assessed by the principal investigator. Adverse event rates were tabulated, and compared between arms via Fisher's exact test.

Efficacy

Tumor response was assessed using standard RECIST v1.1 after every two cycles of therapy. The planned primary endpoint was 1-year PFS rate on each arm. Patients were censored at the time they completed or were removed from study treatment, due to an unacceptable adverse event, per investigator or per their preference. Additional secondary endpoints of response rate and overall survival were assessed by Kaplan-Meier curves, taking into account log-rank computations.

Results

Patient Characteristics and Study Drug Dosing

From August 2012 through April 2015, we randomized 25 patients, of whom 24 patients received at least an entire infusion of protocol therapy. The study was thereafter stopped early due to slow accrual associated with increasingly frequent use of pemetrexed as first-line and/or maintenance treatment of patients with metastatic nonsquamous NSCLC at Johns Hopkins. Eighteen patients received carboplatin, paclitaxel, and bevacizumab with metformin followed by bevacizumab and metformin (Arm A); one patient on Arm A required cessation during the first cycle of therapy due to a paclitaxel reaction. This patient was included in the demographic and safety data results (Tables 1, 2) but excluded from the evaluation of efficacy (Tables 3, 4). Six patients received carboplatin, paclitaxel, and bevacizumab followed by bevacizumab maintenance alone (Arm B). Demographic information for all patients by treatment arm can be found in Table 1. All characteristics were fairly well balanced across treatment arms.

Safety and Tolerability

Therapy was well tolerated on both arms, with the spectrum of adverse events reflective of the known toxicities of carboplatin, paclitaxel, and bevacizumab, as well as disease-related complications of lung cancer (Table 2). No adverse events occurred due to metformin on Arm A. The most common grade 3/4 toxicity on Arm A was decreased neutrophil count (53%), whereas on Arm B, both decreased neutrophil count and infusion-related reactions were most commonly seen (33% in both cases). There was one grade 5 toxicity, colonic perforation, leading to death on Arm A during concomitant therapy, which was attributed to bevacizumab therapy.

The median duration of study treatment on Arm A was 29.8 weeks (range 0.7–76), and 16.6 weeks (range 1.6–36) on Arm B ($p = .10$; Table 3). The most common reason for study

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Table 2. Adverse event rate by arm

	Arm A, $n = 19$		Arm B, $n = 6$	
Adverse event	**Grade 3, *n* (%)**	**Grade 4, *n* (%)**	**Grade 3, *n* (%)**	**Grade 4, *n* (%)**
White blood cell count decreased	3 (16)			
Neutrophil count decreased	3 (16)	7 (37)	1 (17)	1(17)
Lymphocyte count decreased	4 (21)		1 (17)	
Febrile neutropenia	1 (5)		1 (17)	
Sepsis		1 (5)		
Appendicitis			1 (17)	
Catheter-related infection	1 (5)			
Hyponatremia	1 (5)		1 (17)	
Hypokalemia	1 (5)		1 (17)	
Hypophosphatemia	2 (11)			
Hyperglycemia	1 (5)		1 (17)	
Nausea	1 (5)			
Vomiting	3 (16)			
Dehydration	2 (11)		1 (17)	
Infusion-related reaction	1 (5)		2 (33)	
Headache	1 (5)			
Neuropathy			1 (17)	
Arthralgia	1 (5)			
Pain in extremity			1 (17)	
Bone pain	1 (5)			
Insomnia	1 (5)			
Back pain	1 (5)			
Colonic perforation[a]				
Hypertension	3 (16)			
Thromboembolic event	2 (11)			

[a]One grade 5 event on Arm A.

Table 3. Therapy characteristics by arm

Characteristic	**Arm A, $n = 18$**	**Arm B, $n = 6$**
Median cycles of combination chemotherapy (range)	5 (1–6)	4 (1–6)
Median cycles of maintenance bevacizumab (range)	3.5 (0–18)	1 (0–8)
Median time on study treatment in weeks (range)	29.8 (0.7–76)	16.6 (1.6–36)
Reasons for study treatment discontinuation, *n* (%)		
Progression of disease	9 (50)	3 (50)
Adverse event	7 (38.9)	2 (33.3)
Patient choice	1 (5.6)	1 (16.7)
Hospitalization	1 (5.6)[a]	0 (0)

[a]Due to colonic perforation related to bevacizumab.

treatment discontinuation on both arms was progression of disease (Table 3).

Efficacy

Response to study treatment was evaluated via radiologist-assessed RECIST v1.1 and is described in Table 4. Partial responses were seen in 10 of 18 patients on Arm A, corresponding to a response rate of 56% (95% CI: 31%–78%), compared with the historical value of 35% ($p = .11$). Partial responses were seen in two of six patients on Arm B, corresponding to a response rate of 33% (95% CI: 6%–76%).

The primary analysis shows that the addition of metformin improved PFS at 1 year, compared with the historical benchmark. The 1-year PFS on Arm A was 47% (95% CI: 25%–88%), with the 95% lower confidence bound greater than 15%, the hypothesized 1-year PFS without metformin. All patients on

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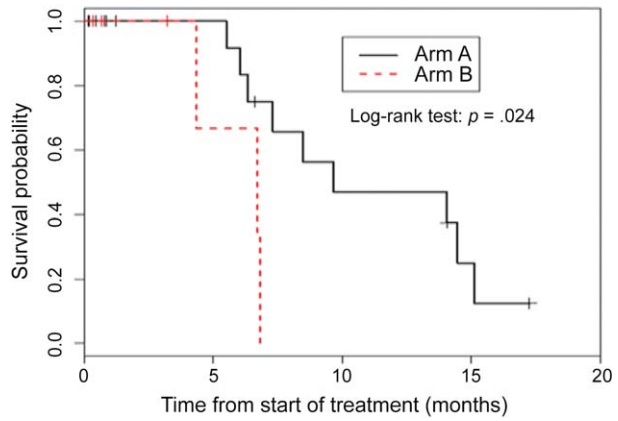

Figure 2. Kaplan-Meier curves for progression-free survival. The analysis included all the patients who received a cycle of study therapy.

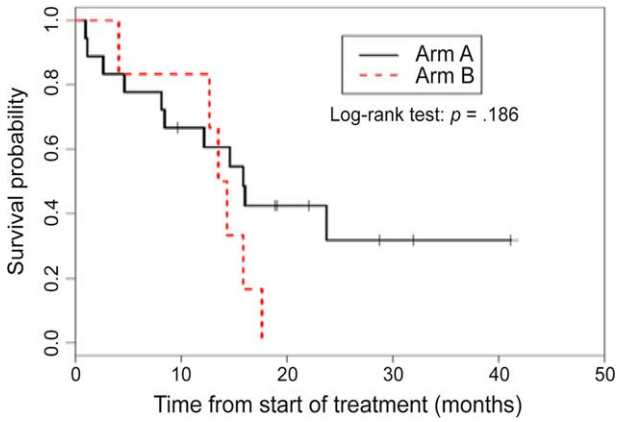

Figure 3. Kaplan-Meier curves for overall survival. The analysis included all the patients who received a cycle of study therapy.

Arm B had progressive disease, were off study due to adverse events, or withdrew by 1 year of follow-up. Patient data was censored at the time of coming off study treatment due to adverse events, as subsequent disease therapies were then administered, making potential contribution of therapeutic benefit of metformin unclear. The PFS distribution between these two arms was significantly different by a log-rank test ($p = .024$). The median PFS was 9.6 months (95% CI: 7.3–not applicable [NA]) for Arm A and 6.7 months (95% CI: 4.4–NA) for Arm B (Fig. 2).

The 1-year OS on Arm A was 68% (95% CI: 48%–92%), compared with the historical probability of 51%. Median OS of patients treated on Arm A was 15.9 months (95% CI: 8.4–NA) and 13.9 months (95% CI: 12.7–NA) on Arm B; the difference was not statistically significant ($p = .186$).

Discussion

To the authors' knowledge, this is the first prospective clinical trial in nondiabetic NSCLC patients to show a significant clinical benefit with metformin in conjunction with carboplatin, paclitaxel, and bevacizumab. The exact mechanism by which this occurred is unclear, and demands further study, as it could potentially benefit a large percentage of patients at some point in their treatment.

Although this trial did not have robust enrollment, demographic characteristics were well balanced and not significantly different. The 1-year PFS in the treatment arm with metformin was found to be significantly higher than 15%, the historical 1-year PFS rate for patients treated with carboplatin, paclitaxel, and bevacizumab [4]. The control arm was included to assess the appropriateness of assuming a historical 1-year PFS of 15%, and all patients assigned to this arm either progressed, were off study for adverse events, or withdrew by 1 year of follow-up. Comparison of the two randomized arms also confirms that PFS is statistically better in the treatment arm with metformin than the control arm without metformin. Although a higher fraction of patients receiving metformin had some response to therapy, the response rates in these two arms were not significantly different, which may be due to the small sample size. Similarly, OS was also found to be nonsignificantly improved in the metformin arm (Arm A). When the results were retrospectively assessed by smoking status and KRAS mutational status, no statistically significant difference in survival status was found.

Caveats are important to consider in interpreting these data. First, and most notably, the sample size was small and the estimates of effect size should therefore be interpreted with caution. The study was stopped after 25 patients because of changes in practice patterns for the treatment of these newly diagnosed nonsquamous NSCLC patients. The small sample size may explain the lack of significant differences in the secondary endpoints of response rate and OS. Importantly, it may also explain the lack of significant differences in toxicity attributable to metformin. Secondly, this initial exploratory study did not include correlative analyses evaluating potential mechanistic effects in patients treated with metformin. The potential antitumor effects of metformin remain to be elucidated. Therapeutic intervention with metformin in cancer is an attractive treatment option, as it is a well-tolerated oral medication with minimal side effects. Metformin 1000 mg b.i.d. was chosen for this study because this dosing schedule has been shown to be safe and effective in the treatment of diabetes, albeit with the understanding that the antitumor effects are not limited to insulin-dependent mechanisms alone. Understanding the mechanisms by which metformin works to regulate tumor growth continues to require further understanding in order to confidently identify the appropriate, and potentially large, treatment population. Finally, it should be noted that one other trial that evaluated the addition of metformin to chemotherapy (gemcitabine and cisplatin) in a similar 30-patient NSCLC population found that it did not significantly affect outcome [20]. However, the dosing of metformin in that trial (500 mg daily) was less than in this trial, as well as in general therapeutic management of diabetes, and as such potentially highlights a dose-dependent component of the clinical effect of metformin. Therefore, further pharmacokinetic and pharmacodynamic evaluation may be needed in subsequent studies.

Further elucidation of the anticancer potential of metformin is ongoing in a multitude of studies across several tumor types, with over 100 active trials on clinicaltrials.gov as of May 2017. This includes evaluation of both preclinical mechanisms as well as later-phase clinical endpoints [15]. In lung cancer,

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mouse models have shown that metformin leads to systemic indirect suppression of receptor tyrosine kinase activation, as well as decreased concentrations of insulin and IGF-1 both in the circulation and in lung tissue, reduced activation of the IR/IGF-1R, decreased downstream signaling, and diminished cancer cell proliferation [21, 22]. NSCLC has also been shown to express the IR, with overexpression found to be predictive of poor survival in patients whom had undergone curative resection [23]. Metformin's effect on liver metabolism is especially interesting in light of the understanding that lung adenocarcinoma has been found to disrupt multiple signaling cascades (Akt, AMPK and SREBP) that alter insulin, glucose, and lipid metabolism in and of itself [24]. A laboratory chemoprevention study reported that metformin treatment reduced lung tumor burden in A/J mice exposed to the tobacco carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) [21]. A/J mice treated with oral metformin after exposure to NNK had lung tumor burden reduced by up to 53% at steady-state plasma concentrations of metformin that are achievable in humans. Even higher levels of tumor burden reduction (72%) were seen when intraperitoneal injections of metformin were used. This dose-related tumor reduction may be an indication of the dose-dependent effects of metformin in NSCLC. In this study, metformin indirectly inhibited mechanistic target of rapamycin (mTOR) in lung tissue by decreasing activation of insulin-like growth factor 1 receptor/insulin receptor and Akt upstream of mTOR.

As the therapeutic focus of NSCLC shifts to immune checkpoint inhibition, further understanding of metformin's immunomodulatory effect on cancer cells must also be taken into account to optimize clinical use [25]. The interaction of metformin and the immune system is also under further study; in mouse models, it was found that a direct effect of metformin on CD-8+ T cells was critical for protection against tumor microenvironment T-cell exhaustion by preventing apoptosis of CD8+ TILs, irrespective of programmed cell death protein 1 (PD-1) and TIM-3 expression [26]. Therefore, further investigation into a possible synergism with checkpoint blockade with or without concurrent chemotherapy is warranted.

Conclusion

Despite the accrual limitations, the results from this study are consistent with the retrospective work described in the introduction as well as the preclinical data described above. We are currently developing a randomized phase II study of metformin with any first-line, platinum-based doublet chemotherapy with or without PD-1 blockade in an attempt to take into consideration provider preference for chemotherapy treatment and develop appropriate peripheral blood and tumor correlative analyses. We believe the thought-provoking data in NSCLC presented in this article are encouraging and should prompt further translational evaluation of metformin as a novel anticancer agent for NSCLC and other solid tumors.

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Disclosures

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The other authors indicated no financial relationships.
(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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