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Addition of Metformin to Concurrent Chemoradiation in Patients With Locally Advanced Non–Small Cell Lung Cancer
The NRG-LU001 Phase 2 Randomized Clinical Trial

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IMPORTANCE Non–small cell lung cancer (NSCLC) has relatively poor outcomes. Metformin has significant data supporting its use as an antineoplastic agent.

OBJECTIVE To compare chemoradiation alone vs chemoradiation and metformin in stage III NSCLC.

DESIGN, SETTING, AND PARTICIPANTS The NRG-LU001 randomized clinical trial was an open-label, phase 2 study conducted from August 24, 2014, to December 15, 2016. Patients without diabetes who were diagnosed with unresectable stage III NSCLC were stratified by performance status, histology, and stage. The setting was international and multi-institutional. This study examined prespecified endpoints, and data were analyzed on an intent-to-treat basis. Data were analyzed from February 25, 2019, to March 6, 2020.

INTERVENTIONS Chemoradiation and consolidation chemotherapy with or without metformin.

MAIN OUTCOMES AND MEASURES The primary outcome was 1-year progression-free survival (PFS), designed to detect 15% improvement in 1-year PFS from 50% to 65% (hazard ratio [HR], 0.622). Secondary end points included overall survival, time to local-regional recurrence, time to distant metastasis, and toxicity per Common Terminology Criteria for Adverse Events, version 4.03.

RESULTS A total of 170 patients were enrolled, with 167 eligible patients analyzed after exclusions (median age, 64 years [interquartile range, 58-72 years]; 97 men [58.1%]; 137 White patients [82.0%]), with 81 in the control group and 86 in the metformin group. Median follow-up was 27.7 months (range, 0.03-47.21 months) among living patients. One-year PFS rates were 60.4% (95% CI, 48.5%-70.4%) in the control group and 51.3% (95% CI, 39.8%-61.7%) in the metformin group (HR, 1.15; 95% CI, 0.77-1.73; $P = .24$). Clinical stage was the only factor significantly associated with PFS on multivariable analysis (HR, 1.79; 95% CI, 1.19-2.69; $P = .005$). One-year overall survival was 80.2% (95% CI, 69.3%-87.6%) in the control group and 80.8% (95% CI, 70.2%-87.9%) in the metformin group. There were no significant differences in local-regional recurrence or distant metastasis at 1 or 2 years. No significant difference in adverse events was observed between treatment groups.

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, the addition of metformin to concurrent chemoradiation was well tolerated but did not improve survival among patients with unresectable stage III NSCLC.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02186847

Visual Abstract
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Survival in locally advanced (LA) non–small cell lung cancer (NSCLC) remains poor; most studies that have attempted to improve outcomes in these patients have been largely unsuccessful.[1,2] However, the Global Study to Assess the Effects of MEDI4736 Following Concurrent Chemoradiation in Patients With Stage III Unresectable Non-Small Cell Lung Cancer (PACIFIC) trial demonstrated that adjuvant immune checkpoint inhibitor therapy after platinum-based chemoradiation improved both progression-free (PFS) and overall survival (OS).[3,4] Although the control group of the PACIFIC trial underperformed compared with historic controls, this study has led to a practice change in LA-NSCLC.

Before the publication of the PACIFIC trial, we initiated NRG-LU001, an international, randomized, phase 2 study in unresectable LA-NSCLC comparing chemoradiation followed by consolidative chemotherapy with the addition of metformin during the delivery of cytotoxic therapy.

Metformin has been studied extensively for its potential antineoplastic effects. This research was prompted by epidemiologic studies showing a reduced incidence of cancer and retrospective case studies showing improved outcomes in patients taking metformin.[5-15] Preclinical data suggested a wide range of antineoplastic effects of metformin, mediated by its ability to stimulate adenosine monophosphate-activated kinase and inhibit the mammalian target of rapamycin pathway.[11,16,17] Indeed, metformin monotherapy exhibits cytostatic and cytotoxic effects both in vivo and in vitro.[18,19] Moreover, individual combinations of metformin and platinum or radiation have shown at least additive effects in multiple preclinical models, including NSCLC.[13,20-24] These clinical and preclinical data, coupled with the well-described safety profile and affordability of metformin, led to NRG-LU001. This study examined prespecified endpoints, and data were analyzed on an intent-to-treat basis.

Key Points

Question Does metformin improve outcomes in nondiabetic, unresectable stage III non–small cell lung cancer (NSCLC) treated with chemoradiation?

Findings In this randomized clinical trial that included 170 patients, survival exceeded expectations in both groups (those who received chemoradiation alone vs chemoradiation and metformin); however, the addition of metformin to chemoradiation did not improve overall or progression-free survival.

Meaning These findings suggest that the addition of metformin to chemoradiation in locally advanced NSCLC is not warranted.

Methods

Study Design and Participants

The NRG-LU001 study was an open-label, randomized, phase 2 trial conducted from August 24, 2014, to December 15, 2016, in patients with unresectable stage IIIA or IIIB NSCLC (per the American Joint Committee on Cancer, 7th ed) eligible for definitive treatment with chemoradiation. This trial was approved by the National Cancer Institute–Cancer Therapy Evaluation Program and Central Institutional Review Board as well as the institutional review board committees at each enrolling institution. Written informed consent was obtained for each patient using a standardized form before study enrollment. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. The trial protocol is available in Supplement 1.

Eligible histology types included adenocarcinoma, adenosquamous, large cell carcinoma, squamous carcinoma (SCC), nonlobar and nondiffuse bronchoalveolar cell carcinoma, or non–small cell lung cancer not otherwise specified. Whole-body positron emission tomography–computed tomography (CT) and brain magnetic resonance imaging were required for staging. Additional inclusion criteria included (1) no personal history of cancer (with the exception of nonmelanoma skin cancer) within the past 3 years, (2) Zubrod performance status (PS) less than or equal to 1 (ie, the patient may be or may not be symptomatic but is completely ambulatory and can carry out light work),[25] and (3) no current diagnosis of diabetes. Central submission of serial blood specimens and baseline tumor biopsies for later analysis was encouraged. Patient race/ethnicity and sex were reported by each participating institution.

Randomization

Following screening and enrollment, patients were randomized (1:1) to receive either 60 Gy of radiation to involved sites combined with concurrent weekly carboplatin and paclitaxel chemotherapy, followed by 2 cycles of consolidative chemotherapy every 3 weeks, or the same regimen combined with metformin during both the concurrent and consolidation phases of cytotoxic therapy. Randomization was based on the Zelen permuted block allocation scheme[26,27] and stratified by PS (0 vs 1), histology (SCC vs non-SCC), and American Joint Committee on Cancer stage (IIIA vs IIIB). Treatment group allocation was performed centrally after confirmation of eligibility and, once assigned, was not blinded.

Treatment and Follow-Up

A total of 60 Gy was delivered in 2-Gy daily fractions Monday through Friday over 30 treatments using either 3-dimensional conformal or intensity-modulated radiation therapy (IMRT). Motion assessment during initial image acquisition at simulation was mandated, as was image guidance with each treatment, the latter via either radiograph or cone-beam CT. Only primary tumor and involved lymph nodes were permitted to be included in the treatment volume. This gross tumor volume was expanded to include respiratory tumor motion during simulation (internal target volume). The internal target volume was then expanded by an additional 0.5 to 1 cm, respecting anatomic barriers to spread, in an effort to generate a clinical target volume, which accounted for microscopic tumor extension. Depending on respiratory motion management and use of image guidance, the clinical target volume was further expanded by an additional 0.5 to 1.5 cm to define the

planning target volume. Each radiation plan was evaluated centrally by the study's principal investigators (H.S. and T.T.) for tumor and normal tissue delineation, planning target volume coverage, and adherence to normal tissue constraints.

Concurrent weekly paclitaxel (50 mg/m^2 per week) and carboplatin (area under the curve [AUC], twice per week) were given during radiation therapy. For this trial, carboplatin was targeted at 2 AUC during radiation therapy and 6 AUC after radiation therapy. Between 28 and 42 days after completion of radiation, paclitaxel (200 mg/m^2) and carboplatin (AUC, 6) were given every 3 weeks for 2 cycles.

The goal dose of metformin was 2000 mg per day orally (500 mg in the morning, 1000 mg at midday, and 500 mg in the evening), with patients required to keep pill diaries to assess compliance. As abrupt dosing at that level is associated with gastrointestinal toxicity, a 2-week metformin dose escalation was built into NRG-LU001. In week 1, patients received 500 mg twice a day; this was increased in week 2 to 500 mg 3 times a day. The beginning of week 3 marked the initiation of chemoradiation and full-dose metformin that continued during concurrent chemoradiation and consolidative chemotherapy. For patients in the experimental group, blood glucose levels were monitored weekly. Metformin dose de-escalation was instituted (by 500-mg steps) if grade 2 or 3 gastrointestinal toxicity was detected. Management of toxicity with loperamide was suggested, and dose re-escalation (at least 2 attempts) was encouraged if toxicity could be kept at less than grade 2.

Follow-up

Follow-up included contrast-enhanced CT or magnetic resonance imaging of the chest and upper abdomen every 3 months in years 1 and 2, every 6 months for years 3 to 5, and annually thereafter. At each imaging point, patients were clinically evaluated by a physician for PS and toxic effects using the Common Terminology Criteria for Adverse Events, version 4.03, recorded at the enrollment site and reported to NRG Oncology.

Statistical Analysis

The primary end point for the study was PFS, defined as the interval between randomization to progression or death, whichever occurred first. Progression was defined using the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, criteria and reported by the participating institution. Secondary end points included OS, local-regional recurrence (LRR), distant metastasis (DM), and toxicity (Common Terminology Criteria for Adverse Events, version 4.03). The study was powered to detect an improvement in 1-year PFS from 50% (no metformin) to 65% (metformin) or, equivalently, a hazard ratio (HR) of 0.622 with a 1-sided type 1 error of 0.1 and 85% power with at least 102 PFS events. With a required 152 patients to be analyzed and an expected 10% rate of ineligibility, the target sample size was set at 168 patients. Analyses were performed on an intent-to-treat basis, with eligible patients included in the assigned treatment arm irrespective of whether they completed the treatment. These outcomes were all analyzed as time-to-event data whose times were measured from randomization. The Kaplan-Meier method was used to estimate PFS and OS rates. A stratified log-rank test was used to compare event rates between treatments, and Cox proportional hazard models were used to evaluate the associations between PFS or OS and treatment as well as other prognostic factors. Incidences of LRR and DM as the first failure were analyzed as competing risks data and estimated using the cumulative incidence method. The competing events of LRR included death without LRR and the development of DM, and the competing events of DM included death without DM and the development of LRR. The corresponding differences in LRR or DM between arms were compared using the Gray test and quantified using the Fine-Gray model.

To control for potential bias in reporting progression in this unblinded study, disease progression was reviewed by the imaging co-chair (J.J.E.), who was blinded to treatment assignment. For each patient, up to 4 image sets (at baseline, 3 months, at progression, and 1 prior to progression) were collected for central review. The PFS based on centrally reviewed progression was analyzed to determine similarity to institutionally reported PFS. Data were analyzed from February 25, 2019, to March 6, 2020. Significance was set at $P < .05$.

Results

Patient and Tumor Characteristics

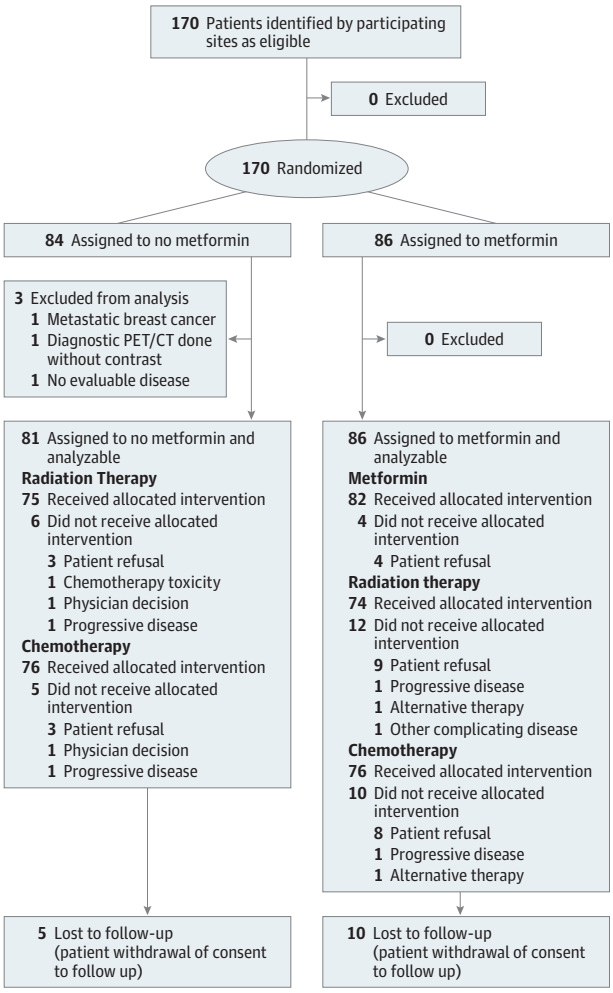
A total of 170 patients were accrued to NRG-LU001 from 79 member institutions in the US, Canada, and Israel. Of the 170 patients, 3 were found to be ineligible for the study after randomization due to (1) a diagnosis of metastatic breast adenocarcinoma, (2) lack of measurable disease at the time of registration, and (3) ineligible baseline imaging (**Figure 1**). The analysis includes all data received at NRG Oncology up to February 25, 2019.

After exclusions, a total of 167 patients were included: 81 in the control group and 86 in the metformin group. The groups were similar in clinical and tumor characteristics, patient age, sex, ethnicity, stage, and histology (**Table 1**). The median age of the study participants was 64 years (interquartile range, 58-71 years), with 97 men (58.1%), 70 women (41.9%)—similar to the sex presentation of this disease generally[28]—and 137 participants (82.0%) were White. Zubrod PS was evenly divided between 0 (83 patients [49.7%]) and 1 (84 patients [50.3%]) in this trial, and 73 patients (43.7%) presented with SCC (Table 1). A total of 54 patients (32.3%) presented with stage IIIB disease; the remaining 110 patients (65.9%) had stage IIIA disease (apart from 3 patients with N2 disease alone [ie, metastasis in ipsilateral mediastinal or subcarinal nodes] staged as TX [ie, cancer location cannot be determined]). Most patients who received radiation (111 [74.5%]) were treated with IMRT, and 139 patients (93.3%) who were treated with radiation received 60 Gy. Four-dimensional CT was used at simulation in 111 (74.4%) of all patients for initial motion assessment, with a similar proportion between groups.

Protocol Adherence

Protocol adherence to treatment is shown in eTable 1 in Supplement 2. Radiation was delivered to 75 patients (92.6%) in the

Figure 1. CONSORT Diagram



National Cancer Institute Cancer Therapy Evaluation Program trials randomize patients while eligibility assessment confirmation is ongoing. CT indicates computed tomography; PET, positron emission tomography.

control group and 74 (86.0%) in the metformin group. Most patients who did not receive radiation either withdrew or refused treatment before initiation. On central review of the radiation treatment plans, 70 patients (97.2%) in the control group and 72 (96.0%) in the metformin group were contoured per protocol. Dose coverage of the primary tumor was per protocol in 47 patients (61.1%) in the control group and 50 (69.4%) in the metformin group, with most remaining plans being minor or acceptable deviations (29% and 28%, respectively). Chemotherapy was delivered per protocol in 127 patients (79.9%) during the concurrent phase and 116 (79.5%) in the consolidation phase, with minimal differences between treatment groups. A total of 52 (63.4%) patients completed the entire course of metformin over the concurrent and consolidative phases of treatment per protocol, with the most common reason for discontinuation being adverse effects from metformin.

Survival Outcomes

Median follow-up was 27.7 months (range, 0.03-47.21 months) among living patients. Survival outcomes are shown in **Table 2** and **Figure 2**. One-year PFS (calculated by institution-reported progression events) was 60.4% (95% CI, 48.5%-70.4%) in the control group and 51.3% (95% CI, 39.8%-61.7%) in the metformin group, with an HR of 1.15 (95% CI, 0.77-1.73; P = .24). Multivariable analysis of PFS including stratification variables and treatment group is shown in eTable 2 in Supplement 2. In this analysis, higher stage was associated with significantly worse PFS (HR, 1.79; 95% CI, 1.19-2.69; P = .005). The remaining variables were not significantly associated with PFS, including treatment group (HR, 1.20; 95% CI, 0.81-1.78; P = .36), histology (HR, 1.24; 95% CI, 0.83-1.85; P = .30), and PS (HR, 0.70; 95% CI, 0.47-1.05; P = .09). Sensitivity analysis for PFS, determined by central review of follow-up imaging, demonstrated similar results (HR, 1.09; 95% CI, 0.69-1.73; P = .36).

In the intention-to-treat analysis, OS was nearly identical between arms (HR, 1.03; 95% CI, 0.64-1.68; P = .89) (Table 2 and Figure 2B). One-year OS was 80.2% (95% CI, 69.3%-87.6%) in the control arm and 80.8% (95% CI, 70.2%-87.9%) in the metformin arm. There were no significant differences in LRR or DM at 1 or 2 years.

In the control group, 30 of 33 deaths (90.9%) were due to disease, whereas this number was 24 of 34 (70.6%) in the metformin group. This discrepancy was due to an increased number of deaths from other causes (2 of 33 [6.1%] vs 4 of 34 [11.8%]) and an unknown cause (1 of 33 [3.0%] vs 6 of 34 [17.6%]). The rates of LRR and DM were also similar between the 2 groups (LRR, HR, 0.91; 95% CI, 0.51-1.62; P = .75 and DM, HR, 1.29; 95% CI, 0.71-2.34; P = .41) (Table 2, Figure 2C and 2D).

Adverse Events

No differences in grade 3 or higher adverse events (AEs) were observed between the control and metformin groups, with 51 patients (68.0%) and 52 patients (65.8%), respectively, exhibiting at least 1 grade 3 AE. All AEs by class and term found in at least 8 of 154 patients (5.2%) are shown in eTable 3 in Supplement 2, whereas the highest-grade toxicity is shown in **Table 3**. A total of 5 grade 5 AEs were reported, including 4 patients in the control group and 1 patient in the metformin group. None were reported as having a potential relationship to treatment. The rates of grade 3 pneumonitis or greater were low (2 patients [2.7%] in the control group and 1 patient [1.3%] in the metformin group).

Discussion

The NRG-LU001 study found no additional toxic effects, but also no survival benefit, when metformin was combined with chemoradiation in LA-NSCLC. However, we did observe better-than-expected 1-year PFS of 60.4%, which was 10% higher than our pretrial estimate based on RTOG 0617.[1] Indeed, this survival outcome compares favorably with the experimental group of the PACIFIC trial, which examined the combination of chemoradiation with consolidation durvalumab, for which 1-year PFS was 55.9%.[3,4]

Table 1. Patient and Tumor Characteristics

Characteristic	No. (%)		
	No metformin (n = 81)	Metformin (n = 86)	Total (n = 167)
Age, y			
≤49	6 (7.4)	3 (3.5)	9 (5.4)
50-59	22 (27.2)	26 (30.2)	48 (28.7)
60-69	29 (35.8)	35 (40.7)	64 (38.3)
≥70	24 (29.6)	22 (25.6)	46 (27.5)
Median (IQR) [range]	64 (58-72) [43-86]	63 (57-70) [47-82]	64 (58-71) [43-86]
Sex			
Male	48 (59.3)	49 (57.0)	97 (58.1)
Female	33 (40.7)	37 (43.0)	70 (41.9)
Race			
American Indian or Alaska Native	2 (2.5)	0 (0.0)	2 (1.2)
Asian	5 (6.2)	2 (2.3)	7 (4.2)
Black or African American	7 (8.6)	7 (8.1)	14 (8.4)
Native Hawaiian or other Pacific Islander	0	1 (1.2)	1 (0.6)
White	67 (82.7)	70 (81.4)	137 (82.0)
More than 1 race	0	1 (1.2)	1 (0.6)
Unknown	0	5 (5.8)	5 (3.0)
Ethnicity			
Hispanic or Latino	3 (3.7)	1 (1.2)	4 (2.4)
Not Hispanic or Latino	77 (95.1)	80 (93.0)	157 (94.0)
Unknown	1 (1.2)	5 (5.8)	6 (3.6)
Zubrod[a] performance status			
0	38 (46.9)	45 (52.3)	83 (49.7)
1	43 (53.1)	41 (47.7)	84 (50.3)
AJCC[b] stage			
IIIA	52 (64.2)	58 (67.4)	110 (65.9)
IIIB	28 (34.6)	26 (30.2)	54 (32.3)
N2, TX	1 (1.2)	2 (2.3)	3 (1.8)
Histology			
Adenocarcinoma	31 (38.3)	42 (48.8)	73 (43.7)
Adenosquamous	1 (1.2)	0	1 (0.6)
Non-small cell lung cancer NOS	11 (13.6)	9 (10.5)	20 (12.0)
Squamous cell carcinoma	38 (46.9)	35 (40.7)	73 (43.7)
Did the patient use cigarettes?			
No (<100 lifetime cigarettes)	5 (6.2)	6 (7.0)	11 (6.6)
Yes, but quit	47 (58.0)	52 (60.5)	99 (59.3)
Yes, currently smoke	22 (27.2)	20 (23.3)	42 (25.1)
Unknown	7 (8.6)	8 (9.3)	15 (9.0)

Abbreviations: AJCC, American Joint Committee on Cancer; IQR, interquartile range; NOS, not otherwise specified.

[a] Zubrod scores range from 0 to 4, with 0 being fully functional and 4 being bedridden.

[b] The American Joint Committee on Cancer IIIA and IIIB staging, which generally indicates the presence of advanced nodal disease and/or a large-volume, locally invasive tumor. Stages are grouped as follows: N2, metastasis in ipsilateral mediastinal or subcarinal nodes; TX, cancer location cannot be determined.

Although in PACIFIC approximately 50% of the patients presented with stage IIIB disease, compared with approximately one-third in the current study, the PFS in NRG-LU001 remains striking, particularly as PACIFIC trial patients were randomized only when progression was not detected after concurrent chemoradiation.

The question of why PFS (and OS) was higher in the current study compared with previous trials remains. The control groups of RTOG 0617 and NRG-LU001 were generally quite similar, apart from NRG-LU001 enrolling more patients with worse PS and slightly more patients with SCC. However, it is unlikely that these differences would account for the improved PFS noted in this study.

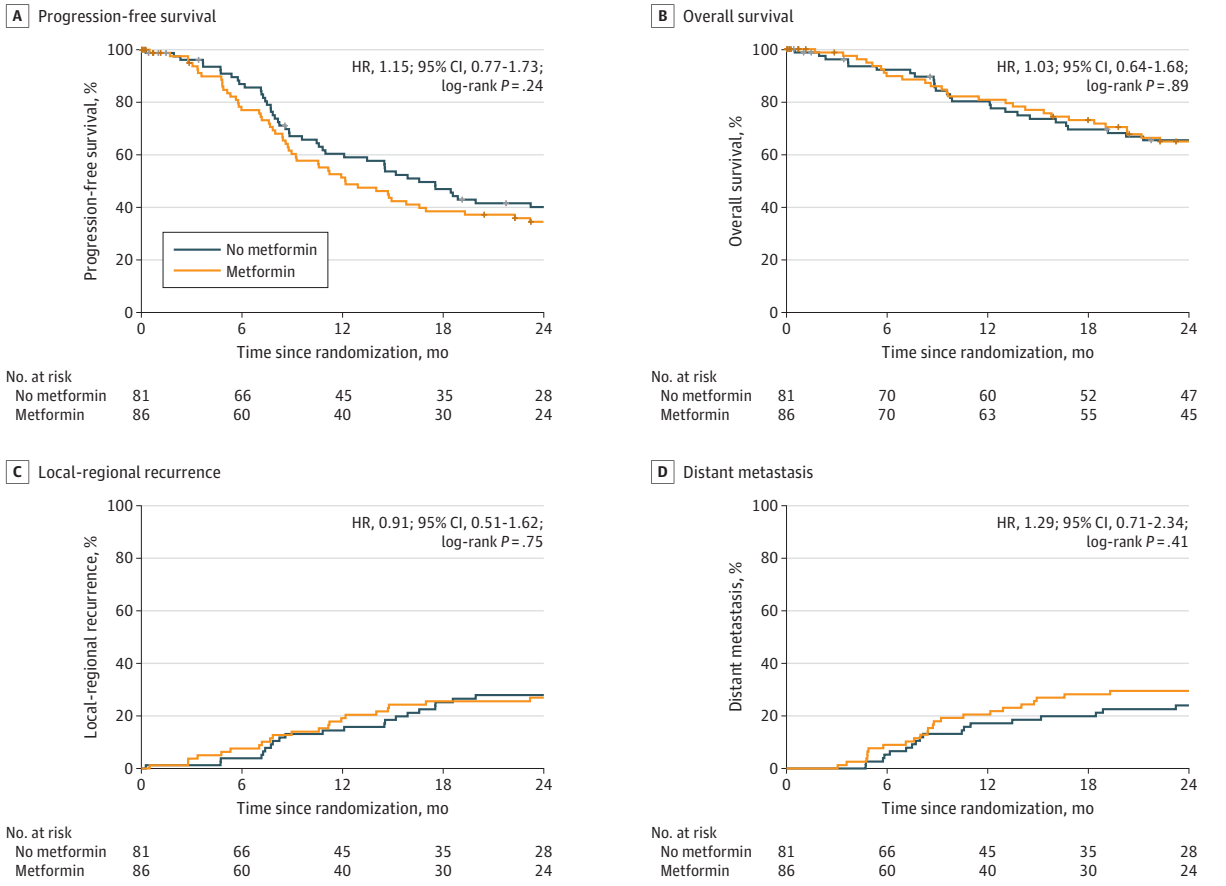
In contrast, 2 additional differences between NRG-LU001 and previous trials may be at play. First, NRG-LU001 excluded patients with preexisting diabetes. Several studies suggest that diabetic patients have worse survival in a variety of malignancies, including lung cancer.[29-31] This could be due to compet-

Table 2. One- and Two-Year Outcomes

Outcome	% (95% CI)		HR (95% CI)	*P* value
	No metformin	Metformin		
At 1 y				
Progression-free survival	60.4 (48.5-70.4)	51.3 (39.8-61.7)	1.15 (0.77-1.73)	.24
Overall survival	80.2 (69.3-87.6)	80.8 (70.2-87.9)	1.03 (0.64-1.68)	.89
Local-regional recurrence	14.5 (7.6-23.4)	19.2 (11.3-28.6)	0.91 (0.51-1.62)	.75
Distant metastasis	17.2 (9.7-26.6)	20.5 (12.4-30.2)	1.29 (0.71-2.34)	.41
At 2 y				
Progression-free survival	40.1 (29.0-51.0)	34.5 (24.2-45.1)	NA	NA
Overall survival	65.4 (53.5-75.0)	64.9 (53.1-74.5)		
Local-regional recurrence	27.9 (18.2-38.4)	27.0 (17.6-37.2)		
Distant metastasis	24.0 (15.0-34.2)	29.5 (19.8-39.9)		

Abbreviations: HR, hazard ratio; NA, not available.

Figure 2. Survival Outcomes and Patterns of Recurrence



HR indicates hazard ratio.

ing risks of death or diminished responses to chemotherapy and radiation in patients with diabetes. The latter may additionally explain the generally consistent improvement in outcome in patients taking metformin seen on retrospective review but its absence in prospective clinical trials.

Second, IMRT was used in 76% of patients in the control group of NRG-LU001, compared with 46% in RTOG 0617. Although improvement in toxicity may be observed via the increased use of IMRT in this setting, it is unclear if IMRT could lead to improved PFS. Use of IMRT could allow for improved coverage of involved areas; however, additional analyses must be performed to address this question. Not only did use of IMRT increase, but the quality of IMRT planning and delivery improved significantly between RTOG 0617 and NRG-LU001, with potential effects on tumor coverage and toxic effects. For instance, although RTOG 0617 had heart dose recommenda-

Table 3. Worst Adverse Events Possibly, Probably, or Definitely Related to Protocol Treatment[a]

Variable	No. (%)	
	No metformin (n = 75)	Metformin (n = 79)
Worst overall grade		
<Grade 3	24 (32.0)	27 (34.2)
≥Grade 3	51 (68.0)	52 (65.8)
<Grade 2	4 (5.3)	5 (6.3)
≥Grade 2	71 (94.7)	74 (93.7)
Worst nausea grade		
<Grade 3	74 (98.7)	77 (97.5)
≥Grade 3	1 (1.3)	2 (2.5)
<Grade 2	54 (72.0)	58 (73.4)
≥Grade 2	21 (28.0)	21 (26.6)
Worst vomiting grade		
<Grade 3	74 (98.7)	78 (98.7)
≥Grade 3	1 (1.3)	1 (1.3)
<Grade 2	66 (88.0)	69 (87.3)
≥Grade 2	9 (12.0)	10 (12.7)
Worst diarrhea grade		
<Grade 3	73 (97.3)	78 (98.7)
≥Grade 3	2 (2.7)	1 (1.3)
<Grade 2	67 (89.3)	65 (82.3)
≥Grade 2	8 (10.7)	14 (17.7)
Worst pneumonitis grade		
<Grade 3	73 (97.3)	78 (98.7)
≥Grade 3	2 (2.7)	1 (1.3)
<Grade 2	63 (84.0)	67 (84.8)
≥Grade 2	12 (16.0)	12 (15.2)

[a] Adverse events were graded with Common Terminology Criteria for Adverse Events, version 4.03.

tions, NRG-LU001 used specific heart constraints for several variables, including V30 (ie, the percentage of the heart receiving at least 30 Gy), which has recently been shown to be associated with OS in RTOG 0617.[2] Although few acute cardiac events were observed in NRG-LU001 related to therapy (1 grade-3 cardiac toxicity in each group), long-term outcomes remain to be seen.

Finally, in NRG-LU001, all radiation treatment plans were subjected to centralized review, and the vast majority of patients who received radiation were treated per protocol. Several studies have highlighted the importance of radiation quality in patient outcome,[2,32] making this type of review critical for clinical trials involving radiation.

Central review of imaging defining progression was also performed. The NRG-LU001 study did not include a placebo control owing to the high cost of adding a placebo compared with the modest cost of metformin itself. Moreover, a placebo control could limit the ability of community sites to accrue, partially defeating the purpose of an inexpensive and pragmatic trial. Thus, to control for any bias in assessment of disease progression by participating institutions based on treatment group, a blinded review of CT images defined as progression as well as preceding images were reviewed centrally (J.J.E.). The PFS calculated based on central review was not different compared with participating center results, indicating that such bias did not influence the results of this study.

Recently, initial results were reported from a Canadian randomized trial (Ontario Clinical Oncology Group [OCOG]-Advanced Lung Cancer Treatment With Metformin and Chemoradiotherapy [ALMERA]) that added metformin to concurrent chemoradiation in LA-NSCLC followed by consolidation metformin for 1 year. Although it closed early owing to slow accrual, OCOG-ALMERA study investigators found metformin to be associated with increased toxic effects and worse survival, whereas its control group outcomes were similar to both groups of NRG-LU001.[33] The explanation for these findings is unclear and bears further analysis.

There are several possibilities to explain these findings in the context of data pointing to the antineoplastic effects of metformin.[34,35] First, the retrospective data are subject to biases inherent to such studies, particularly being drawn from a population with diabetes. Thus, any antineoplastic effect of metformin observed in this setting could be explained by its metabolic benefits in patients with diabetes. Additionally, despite many analyses supportive of the antineoplastic effects of metformin, this finding is not uniform.[36-40] Furthermore, many, but not all, preclinical studies used concentrations of metformin thought to be difficult to achieve clinically.[41]

It is still uncertain whether metformin will have a use in the management of lung cancer in the future. The drug does exert an effect on tumor metabolism in patients with NSCLC.[42] Moreover, a recent phase 2 randomized trial combining metformin with tyrosine kinase inhibitors in NSCLC showed significant improvement in survival compared with tyrosine kinase inhibitors alone, albeit using a lower dose of metformin (1000 mg daily).[43] Furthermore, emerging data suggest that metformin may augment immune checkpoint blockade, leading to ongoing trials combining programmed cell death protein 1– and programmed death-ligand 1–driven therapy and metformin.[44-47]

Limitations

This study has limitations. Approximately two-thirds (63.2%) of patients in the experimental group received metformin per protocol, but only 39% of patients were able to maintain oral metformin intake at the indicated dose without modifications. Thus, compliance and patient tolerance of metformin was an additional variable affecting these results. This is a topic currently under investigation. In addition, this study was not placebo controlled primarily owing to cost restrictions. This fact was addressed by using central imaging review to confirm individual institution reported progression; however, the absence of a placebo remains a limitation.

Conclusions

In conclusion, the addition of metformin to concurrent chemoradiotherapy and consolidation chemotherapy did not improve survival outcomes for patients with LA-NSCLC in this randomized clinical trial. Survival outcomes in this patient population were excellent compared with data from previous randomized clinical trials.

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