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A pooled analysis of two phase II trials evaluating metformin plus platinum-based chemotherapy in advanced non-small cell lung cancer

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ABSTRACT

Background: Despite a wealth of preclinical and observational data, prospective data regarding the use of metformin in lung cancer is extremely limited.
Methods: We pooled individualized data from two prospective trials evaluating metformin plus platinum-based chemotherapy, with or without bevacizumab, in non-diabetic patients with untreated advanced NSCLC. In addition to reporting on clinical efficacy and safety endpoints, we also explored metformin's activity in key molecular cohorts.
Results: 33 patients were included in the pooled analysis, of whom 70% were current or previous smokers. 82% had standard tissue molecular testing results available. KRAS, EGFR, and LKB1 mutation prevalence was 48%, 26%, and 8.3%, respectively. Composite median PFS was 6 months for all patients (95% CI: [1.36, 7.96]), 7.2 months for KRAS mutants (95% CI: [1.18, 9.21]), and 6.6 months for EGFR mutants (95% CI: [1.18, 15.29]). Composite median OS was 14.8 months for all patients (95% CI: [8.25, 19.99]), 17.5 months for KRAS mutants (95% CI: [8.86, 26.96]), and 13.3 months for EGFR mutants (95% CI: [2.60, 25.86]). Lymphopenia was the most common grade 3 AE (12%), followed by leukopenia, nausea, vomiting, and hypertension (9% each). There were 2 grade 4 AEs, neutropenia (21%) and sepsis (3%), and 1 grade 5 AE (colonic perforation) attributed to bevacizumab.
Conclusion: Our results confirm the previously shown efficacy and tolerability of metformin in combination with chemotherapy and highlight encouraging activity in key molecular cohorts. Future efforts should build on this work by prospectively studying metformin in these molecular subgroups.

Introduction

Metformin, a well-tolerated and effective oral medication used to treat non-insulin-dependent diabetes mellitus, is one of the most commonly prescribed medications worldwide. Metformin lowers serum glucose levels by inhibiting gluconeogenesis in the liver as well as by enhancing peripheral insulin sensitivity. As our understanding of the link between metabolism and carcinogenesis evolves, interest in studying the anti-neoplastic properties of metformin continues to grow, particularly in non-small cell lung cancer (NSCLC).

The mechanism by which metformin affects cancer cells is still being elucidated in preclinical models. Recent work suggests that metformin antagonizes “energy-sensing” pathways important for cell growth and proliferation by activating AMP-activated protein kinase (AMPK) and the IGF1-insulin axis [1]. Activated AMPK, a master regulator of cellular metabolism, can inhibit downstream signaling pathways including the P13K/AKT/MTOR pathway. In vivo, metformin has also been shown to inhibit mitochondrial complex I and prevent subsequent oxidative phosphorylation, thereby blocking a necessary step for uncontrolled tumor cell growth [2]. More recently, metformin has been shown to increase the number of CD8+ tumor-infiltrating lymphocytes (TILs) in several tumor cell lines including NSCLC, uncovering a potential role in enhancing immune cell activation [3].

Robust preclinical studies involving both cell lines and mouse models have demonstrated metformin's anti-proliferative effects [4,5]. This work has been supported by clinical observational data showing

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Table 1
Baseline characteristics and mutation status for each patient in this pooled analysis. Abbreviations: A: trial A patient; B: trial B patient; M, male; F, female; Mut, mutant; WT, wild type; N/A, not applicable.

Patient	Age	Sex	Smoking History	KRAS	LKB1 (STK11)	EGFR	Other mutations
A1	77	M	Yes	Mut	WT	WT	JAK3
A2	69	F	Yes	Mut	WT	WT	BRAF non-V600E, CTNNB1, FBXW7, FGFR3, TP53
A3	66	M	Yes	Mut	WT	WT	None
A4	61	M	No	WT	N/A	Mut (exon 20)	None
A5	67	M	Yes	Mut	WT	WT	None
A6	66	F	No	WT	WT	WT	ERBB2, PTEN
A7	75	M	Yes	WT	N/A	WT	None
A8	53	F	Yes	WT	WT	Mut (exon 20)	CDKN2A
A9	65	F	Yes	WT	WT	Mut (exon 21)	MET, TP53
A10	71	M	Yes	Mut	WT	WT	KIT
A11	62	F	Yes	WT	WT	WT	TP53
A12	61	F	No	Mut	WT	WT	None
A13	71	F	Yes	Mut	N/A	WT	None
A14	70	F	No	WT	WT	WT	None
B1	55	F	Yes	N/A	N/A	N/A	N/A
B2	71	F	Yes	Mut	N/A	WT	None
B3	64	F	No	Mut	N/A	WT	None
B4	44	F	No	WT	Mut (LKB1 loss)	Mut (exon 19)	ERBB2, Her2, p53, RB
B5	66	M	No	WT	N/A	WT	BRAF V600E
B6	37	M	No	Mut	N/A	Mut (exon 3)	None
B7	48	F	No	WT	N/A	Mut (exon 20)	None
B8	44	M	Yes	WT	N/A	WT	None
B9	63	F	Yes	WT	N/A	WT	BRAF V600E, PI3KCA
B10	68	F	No	WT	N/A	Mut (exon 18)	p53
B11	47	F	Yes	Mut	N/A	WT	None
B12	60	M	Yes	Mut	N/A	WT	None
B13	60	M	Yes	N/A	N/A	N/A	N/A
B14	64	M	Yes	N/A	N/A	N/A	N/A
B15	74	F	Yes	N/A	N/A	N/A	N/A
B16	55	F	Yes	Mut	N/A	WT	None
B17	54	F	Yes	N/A	N/A	N/A	N/A
B18	73	M	Yes	N/A	N/A	N/A	N/A
B19	61	F	Yes	WT	N/A	WT	None

the therapeutic and chemo-preventive benefits of metformin use in diabetic patients with various malignancies, including breast, prostate, and ovarian cancer [6–14]. Included in this observational data is a meta-analysis of diabetic patients with all stages of lung cancer, which revealed that use of metformin led to significant improvements in both progression-free survival (PFS, HR 0.65, 95% CI = 0.52–0.83) as well as overall survival (OS, HR 0.78, 95% CI = 0.64–0.93) in these patients [15]. Recently, two small prospective trials evaluating metformin in combination with platinum-based doublet chemotherapy demonstrated encouraging outcomes in patients with treatment-naïve, advanced NSCLC [16,17]. In addition, a randomized phase II study demonstrated improvements in response rate (RR), PFS and OS with the addition of metformin to 1st or 2nd generation tyrosine kinase inhibitor (TKI) therapy compared to TKI monotherapy in advanced NSCLC with mutated epidermal growth factor receptor (EGFR), further highlighting the potential benefit of metformin in oncogene-mutated NSCLC [18].

Despite substantial preclinical and observational data, very few prospective trials have evaluated metformin in lung cancer. Given the need to further characterize metformin's therapeutic value and safety in larger data sets, we conducted a pooled analysis of individualized data from two phase II trials, with a focus on metformin's activity in specific molecular cohorts, including patients with EGFR and KRAS mutations. To our knowledge, this analysis represents the largest prospective cohort evaluating the use of metformin with platinum-based chemotherapy in advanced NSCLC.

Methods

Study population

Two phase II trials (trial A [NCT02019979] and trial B [NCT01578551]) were incorporated in this analysis [16,17] Both studies included adults with histologically-confirmed stage IV, treatment-naïve, non-squamous (NS)-NSCLC with a preserved performance status (ECOG PS 0–2) and measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Trial A excluded patients with sensitizing EGFR mutations for whom targeted therapy would be the standard of care and those patients with prior metformin use within the past 6 months. Trial B allowed patients with activating EGFR mutations who had received prior oral EGFR inhibitor therapy. Exclusion criteria for trial B included uncontrolled hypertension (>150/>100 mmHg), use of chronic therapeutic-dose anticoagulation or chronic full-dose aspirin (≥325 mg/day), or history of gross hemoptysis, thrombosis, or hemorrhage. Patients with previous or current diabetes (of any type) or untreated brain metastases were excluded from both studies.

Study protocol

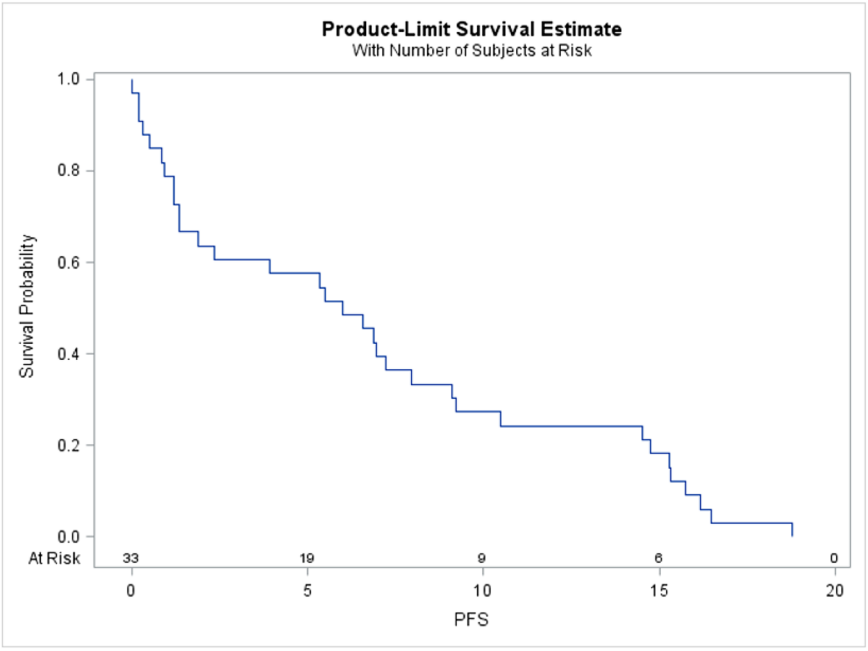
Trial A was a single-arm open-label phase II trial in which all patients received chemotherapy with metformin. Chemotherapy in this study consisted of carboplatin AUC 5 + pemetrexed 500 mg/m2, both given intravenously (IV) on day 1 every 21 days for 4 cycles. Maintenance pemetrexed was given as above for patients with at least stable disease and was continued until disease progression or intolerance. Metformin was started at 500 mg orally (PO) twice daily (BID) for 1 week beginning on day 1 of cycle 1 of chemotherapy (C1D1) and was increased by 500 mg/day on C1D8 and again on C1D15 to achieve a final dose of 1000 mg PO BID. Metformin therapy was continued until disease progression or intolerance.

Trial B was an open-label phase II trial in which patients were randomized 3:1 to receive chemotherapy with or without metformin, respectively. Chemotherapy in this study consisted of carboplatin AUC 6 + paclitaxel 200 mg/m2 + bevacizumab 15 mg/kg, all given IV on day 1 every 21 days for 4–6 cycles. Patients with at least stable disease

went on to receive maintenance bevacizumab 15 mg/kg IV every 21 days until disease progression or intolerance. Patients on the experimental arm were simultaneously treated with metformin, with dose escalation as in trial A to achieve a final dose of 1000 mg PO BID. Only patients randomized to the metformin arm in trial B were included in this pooled analysis.

Because metformin is thought to be cytostatic as opposed to cytotoxic, the primary endpoint in this analysis is clinical efficacy as measured by composite PFS. Overall survival (OS) and tolerability as measured by composite incidence of adverse events (AE) were the secondary endpoints. When available, molecular analysis was performed on biopsy specimens per standard of care and institutional guidelines. Molecular analysis was done using commercially available ion torrent next-generation sequencing panels in trial A, whereas in trial B an institutional lung cancer gene panel was utilized. Subset analysis of outcomes segregated by mutational status was carried out as below. Informed consent for participation was obtained from every patient and each trial protocol was individually considered and approved by the respective Institutional Review Board (IRB).

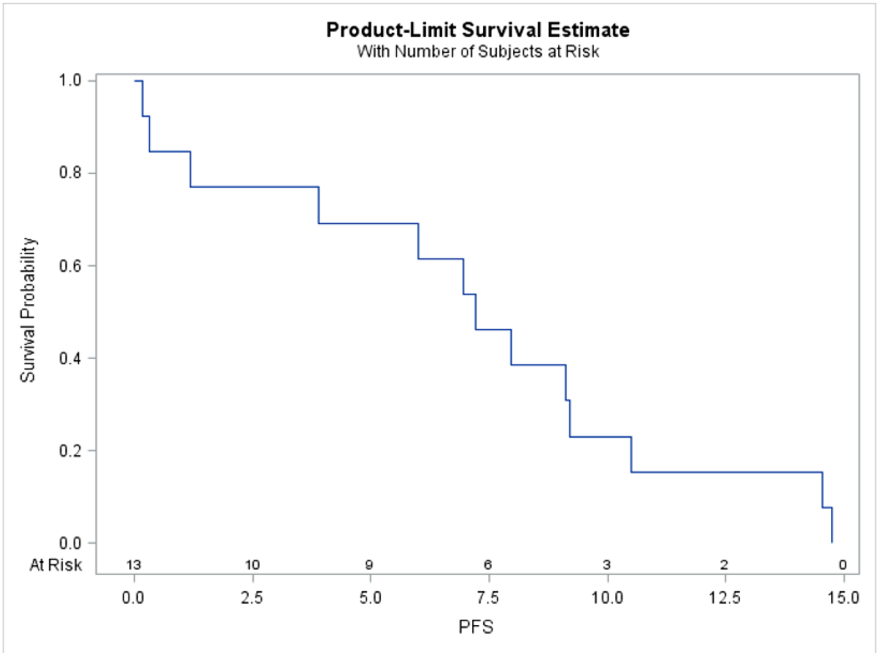
PFS for All Patients



Median PFS (mos): 6.00

(95% CI: [1.36, 7.96]

PFS in KRASm Subgroup



Median PFS (mos): 7.21

(95% CI: [1.18, 9.21]

Fig. 1. Kaplan–Meier (KM) estimates for progression-free survival (PFS) in months (mos), for all patients and also stratified by molecular subgroups. Abbreviations: KRASm, patients with KRAS mutations; EGFRm, patients with EGFR mutations; CI, confidence interval.

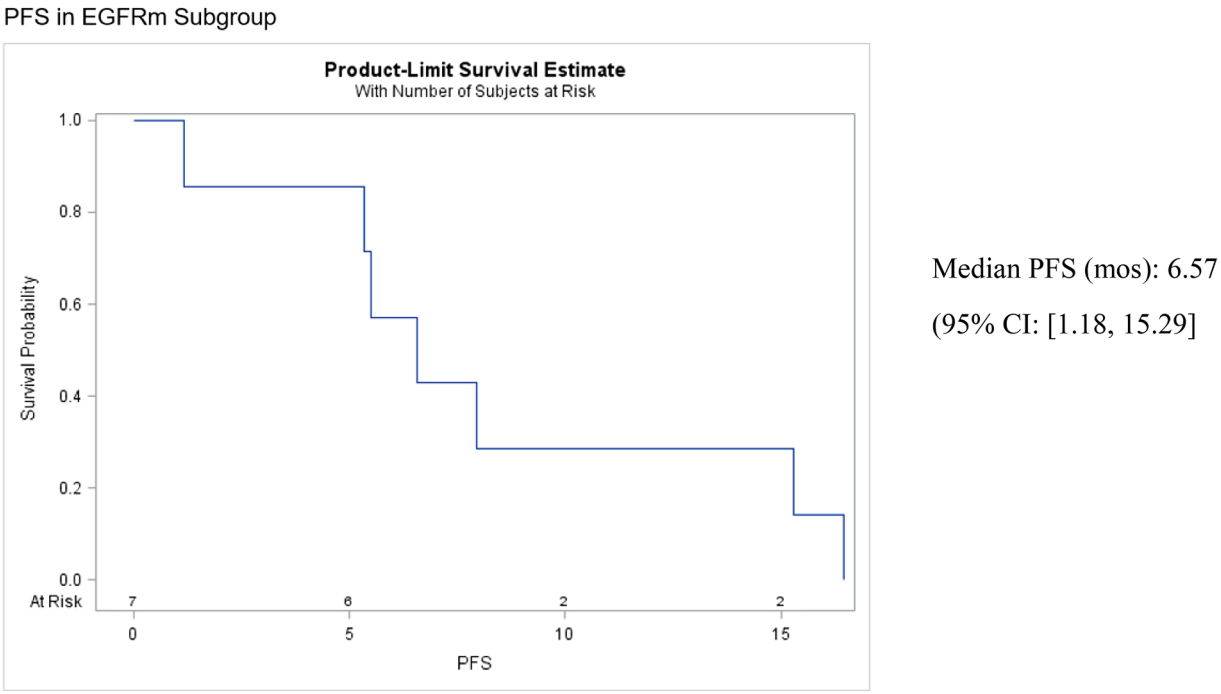


Fig. 1. (*continued*)

Response assessment

Safety assessment including history and physical examination as well as routine bloodwork was performed for all patients at screening and at least once per cycle on day 1, with more frequent assessments done as needed. All adverse events were coded according to Common Terminology Criteria for Adverse Events (CTCAE) v4.0 and any necessary dose reductions were made by the treating physician per study protocol. Response assessment was done radiographically with either computed tomography (CT) or positron emission tomography (PET) scans after every 4 cycles in trial A, whereas such assessments were done after every 2 cycles in trial B. Earlier response assessments were done at the treating physician's discretion if concerning symptoms developed. All responses were measured compared to baseline imaging and were assessed as per RECIST v1.1 criteria.

Statistics and outcomes analysis

All data from both trials were combined manually by study investigators and baseline demographic information and safety/AE data were summarized using standard descriptive statistics. The primary endpoint, composite PFS, was defined as the time from C1D1 to either first disease progression per RECIST v1.1 or death from any cause (PFS definition in trial A), or study treatment discontinuation for any reason (PFS definition in trial B). PFS for patients who did not meet any of these criteria and who were alive at the data analysis cutoff point was censored at the date of the last evaluable tumor assessment. The secondary endpoint of composite OS was defined as the time from C1D1 to day of death from any cause. OS for patients who were alive at the data analysis cutoff point was censored at the last known date of study contact. Kaplan–Meier (KM) curves were generated from the pooled data to estimate the distribution of PFS and median time to PFS as well as corresponding 95% confidence intervals (CIs) via Greenwood's formula. Similar analytic approaches were employed to analyze OS from the combined data. Mutational profiles for each case were obtained through next-generation sequencing of tumor tissue and any relevant differences in outcomes were noted as below.

Results

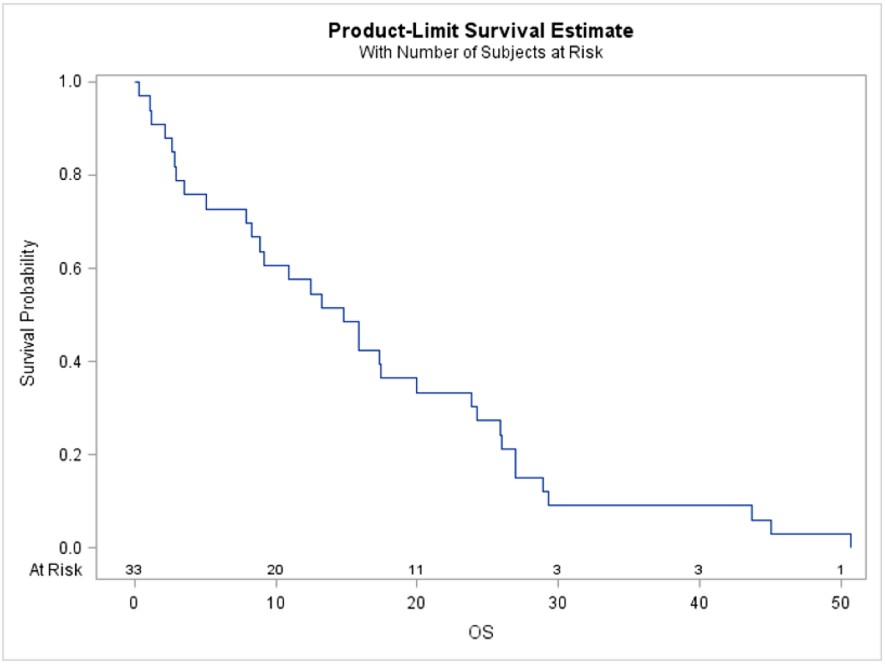
Patient demographics

A total of 33 patients were included in this pooled analysis. The 14 patients from trial A were enrolled at three clinical sites from January 2014 to April 2016, while the other 19 patients from trial B were enrolled at one clinical site from August 2012 to April 2015. Baseline demographic characteristics as well as mutational profiles for each patient are summarized in Table 1. 61% of the study participants were women and the mean age for this cohort was 62 years. The vast majority of patients were either Caucasian (67%) or African–American (21%), while 3% were Asian. 70% of the population were current or previous smokers. 82% of the total cohort had standard molecular testing results available. Of these, 48% harbored KRAS mutations and 26% had EGFR mutations. Among the 12 patients whose tumors were tested for LKB1 status, 1 mutation was identified (8.3%). By design, none of the trial A patients with EGFR mutations received TKI therapy prior to enrollment, including the 1 patient with a sensitizing mutation, which was discovered later in their clinical course. Of the 4 trial B patients with EGFR mutations, only the 1 patient with a sensitizing mutation received initial TKI therapy. 15% of patients had no mutations identified during tissue molecular analysis.

Clinical efficacy

The primary endpoint of composite median PFS for all patients in this pooled analysis was 6 months (95% CI: [1.36, 7.96]) with the addition of metformin to platinum-based chemotherapy with or without bevacizumab. Subgroup analysis conducted via molecular stratification revealed a composite median PFS of 7.2 months (95% CI: [1.18, 9.21]) for patients with KRAS mutations and 6.6 months (95% CI: [1.18, 15.29]) for patients with EGFR mutations. The secondary endpoint of composite median OS for all patients was 14.8 months (95% CI: [8.25, 19.99]). Subgroup analysis revealed a composite median OS of 17.5 months (95% CI: [8.86, 26.96]) for patients with KRAS mutations and 13.3 months (95% CI: [2.60, 25.86]) for patients with EGFR mutations. Kaplan–Meier curves for clinical efficacy endpoints for the total

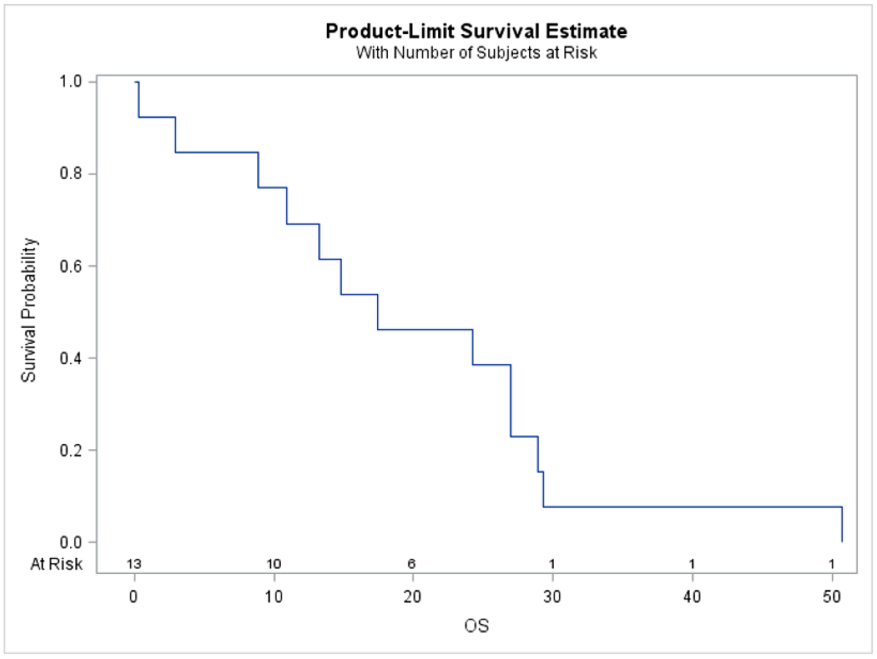
OS for All Patients



Median OS (mos): 14.83

(95% CI: [8.25, 19.99]

OS in KRASm Subroup



Median OS (mos): 17.46

(95% CI: [8.86, 26.96]

Fig. 2. Kaplan–Meier (KM) estimates for overall survival (OS) in months (mos), for all patients and also stratified by molecular subgroups. Abbreviations: KRASm, patients with KRAS mutations; EGFRm, patients with EGFR mutations; CI, confidence interval.

population as well as for key molecular cohorts are shown in Fig. 1 (PFS) and Fig. 2 (OS).

Safety

The addition of metformin to chemotherapy with or without bevacizumab was well-tolerated by patients in this pooled cohort. All trial A patients achieved the maximum metformin dose of 1000 mg PO BID over the 2 week escalation period save for 1 patient, who died prematurely from a cause unrelated to medication toxicity. All trial B patients also achieved the maximum metformin dose of 1000 mg PO BID. Safety/tolerability was assessed by the secondary endpoint of composite incidence of adverse events (AEs), and Table 2 shows the most common serious (CTCAE Grade 3/4/5) AEs. Decreased lymphocyte count was the most common grade 3 AE, experienced by 12% of patients. Decreased white blood cell count, decreased neutrophil count, nausea, vomiting, and hypertension were the next most common grade 3 AEs, at 9% each. There were 2 recorded grade 4 AEs, decreased neutrophil count (21%) and sepsis (3%). There was 1 grade 5 AE for colonic perforation in a trial B patient, which was attributed to treatment with bevacizumab.

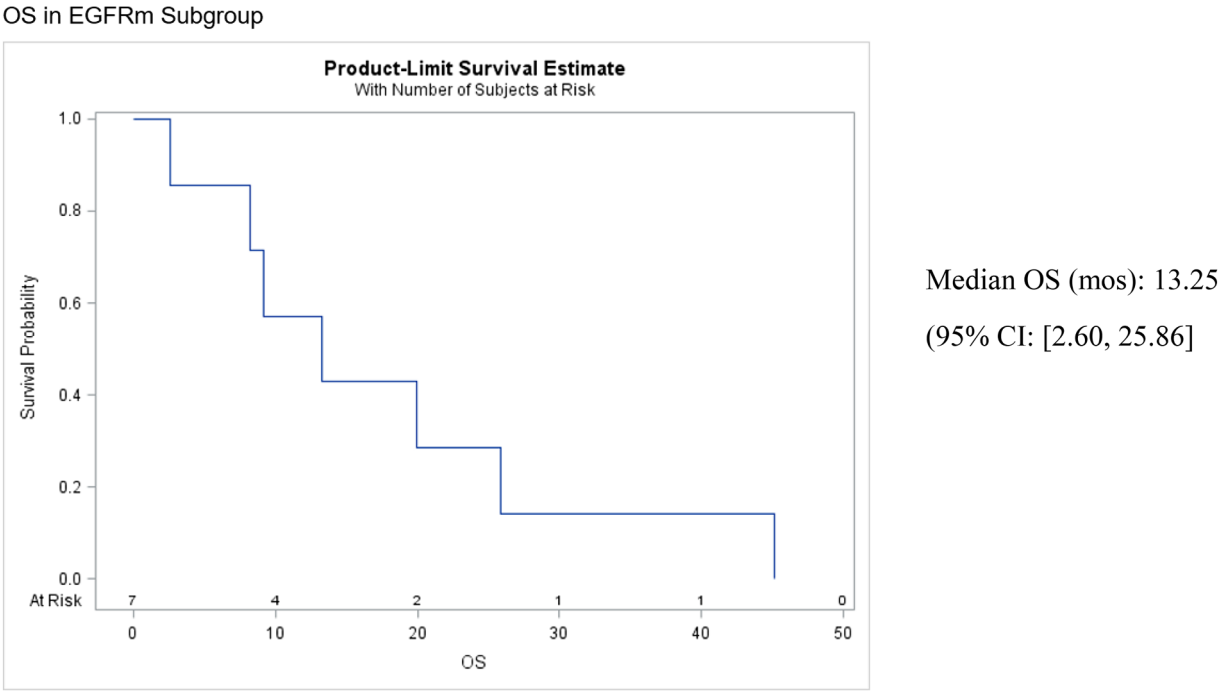


Fig. 2. (*continued*)

Table 2
Common serious (Grade 3/4/5) adverse events (AEs). Graded by Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

	Grade 3 *n* (%)	Grade 4 *n* (%)	Grade 5 *n* (%)
White blood cell decreased	3 (9)		
Neutrophil count decreased	3 (9)	7 (21)	
Lymphocyte count decreased	4 (12)		
Febrile neutropenia	1 (3)		
Sepsis		1 (3)	
Catheter-related infection	1 (3)		
Hyponatremia	1 (3)		
Hypokalemia	1 (3)		
Hypophosphatemia	2 (6)		
Hyperglycemia	1 (3)		
Nausea	3 (9)		
Vomiting	3 (9)		
Dehydration	2 (6)		
Infusion-related reaction	1 (3)		
Headache	1 (3)		
Arthralgia	1 (3)		
Bone pain	1 (3)		
Insomnia	1 (3)		
Back pain	1 (3)		
Colonic perforation			1 (3)
Hypertension	3 (9)		
Thromboembolic event	2 (6)		
Dyspepsia	1 (3)		

Discussion

Drug repositioning, or the use of an established and approved medication to treat a different disease, is an increasingly employed strategy to circumvent the time and resources required for novel drug development. This is especially true within oncology, where commonly used drugs such as aspirin and statins have been shown in many pre-clinical and clinical studies to have both preventive and therapeutic effects in various types of cancer [19–28]. Similarly, substantial evidence supports metformin's anti-neoplastic potential, but much of the clinical data is retrospective and observational. In this study, we evaluated metformin in a pooled analysis of two recent prospective trials including non-diabetic patients with lung cancer. To our knowledge, this analysis represents the largest prospective study of metformin plus platinum-based chemotherapy in treatment-naïve, advanced NSCLC.

In this study, the primary endpoint of composite median PFS was found to be 6 months. This estimate represents a significant improvement compared to historical controls of platinum-based chemotherapy regimens alone, and is commensurate with more recent historical control regimens containing bevacizumab [29–32]. In addition, the composite median OS of 14.8 months represents an improvement compared to historical controls prior to the advent of immunotherapy in driver mutation-negative patients. These results are certainly limited by the overall small number of patients included in this analysis, and are also likely influenced by the relatively high prevalence of KRAS mutations (48%), which are thought to connote a worse prognosis in NSCLC [33]. Nonetheless, these results help confirm previously reported findings that metformin has clinical efficacy, is well tolerated, and may be a useful adjunctive therapy in this setting.

We also explored the efficacy of metformin when added to standard chemotherapy in key molecular cohorts, namely patients carrying KRAS or EGFR mutations. The composite median PFS for patients with KRAS and EGFR mutations was found to be 7.2 months and 6.6 months, respectively. The composite median OS for these same subgroups was 17.5 months and 13.3 months, respectively. Of the seven patients with EGFR mutations in this cohort, two carried sensitizing mutations in either exon 19 or exon 21, while four carried non-sensitizing mutations in either exon 18 or exon 20. The one remaining patient had a rare exon 3 mutation (R98Q), the prognostic implications of which are currently unknown [34]. Thus, our results show that metformin may be particularly effective in patients with KRAS mutations as well as in patients with non-sensitizing EGFR mutations. Further translational work will be needed to better understand the specific activity witnessed in these genotypes.

At the outset of our analysis we also hoped to explore the efficacy of metformin in patients with somatic mutations in the tumor suppressor gene LKB1. Also known as STK11, LKB1 is inactivated in up to 30% of all NSCLC cases, commonly occurs alongside KRAS, and has been identified as a potential biomarker to predict response to metformin therapy [35–38]. Unfortunately, at least in part due to incomplete molecular testing in our cohort (64% of patients [$n = 21$] were not

Table 3
Current trials evaluating metformin use in lung cancer. Completed and terminated studies are not included in this table. Trial status is as of January 9, 2019.

Official title and identifier	Patient population	Trial arms	Locations	Trial status
A Phase II Study to Investigate a Combination of Metformin with Chemo-Radiotherapy in Patients with Locally Advanced NSCLC (ALMERA) [NCT02115464]	Untreated Stage III NSCLC	Concurrent ChemoRT + Metformin vs Concurrent ChemoRT	Canada (AB, ON, MB, QC)	Currently Recruiting
Randomized Phase II Trial of Concurrent Chemoradiotherapy ± Metformin HCl in Locally Advanced NSCLC [NCT02186847]	Untreated Stage III NSCLC	Concurrent ChemoRT + Metformin vs Concurrent ChemoRT	USA, Canada, Israel (Many Sites)	Active, No Longer Recruiting
Tumor Mutation Status will Predict Metabolic Response to Metformin in NSCLC [NCT02285855]	All Stages of NSCLC with Intent to Treat with SBRT	SBRT + Metformin vs SBRT + Placebo	USA (TX)	Active, No Longer Recruiting
A Pilot Study of Metformin as a Chemoprevention Agent in NSCLC [NCT01717482]	Untreated Stage I-IIIA squamous NSCLC	Metformin vs Observation	USA (MN)	Active, No Longer Recruiting
Effect of Metformin in Combination with Tyrosine Kinase Inhibitors on Clinical, Biochemical, and Nutritional Status in Patients with NSCLC: a Randomized Clinical Trial [NCT03071705]	EGFR-Mutant NSCLC	TKI + Metformin vs TKI	Mexico (DF)	Currently Recruiting
A Pharmacodynamic Study of Sirolimus and Metformin in Patients with Advanced Solid Tumors [NCT02145559]	Unresectable or Metastatic NSCLC Refractory to Standard Treatment Options	Sirolimus + Metformin vs Sirolimus + Delayed Metformin	USA (IL)	Active, No Longer Recruiting
Exploiting Metformin Plus/Minus Cyclic Fasting Mimicking Diet (FMD) to Improve the Efficacy of Platinum-Pemetrexed Chemotherapy in Advanced LKB1-inactive Lung Adenocarcinoma: the FAME Trial [NCT03709147]	Unresectable Stage III & Stage IV LKB1-inactive Lung Adenocarcinoma	Chemotherapy + Metformin + FMD (diet) vs Chemotherapy + Metformin	Italy (Milan)	Active, Not Yet Recruiting
Phase II Study of Single-Agent Pre-operative Metformin in Patients with Clinical Stage I-IIIA NSCLC Proceeding to Surgical Resection (LUNG METCORE) [NCT03086733]	Untreated Stage I-IIIA NSCLC	Metformin	Canada (ON)	Currently Recruiting
Trial of Behavioral Weight Loss and Metformin Treatment to Lower Insulin Growth Factor in Cancer Survivors (SPIRIT) [NCT02431676]	Lung Cancer s/p Curative-Intent Therapy	Self-Directed Behavioral Weight Loss vs Coach-Directed Behavioral Weight Loss vs Metformin	USA (MD)	Active, No Longer Recruiting
Parallel Proof of Concept Phase 2 Study of Nivolumab and Metformin Combination Treatment in Advanced NSCLC with and Without Prior Treatment with PD-1/PD-L1 Inhibitors [NCT03048500]	Unresectable Stage III & Stage IV NSCLC	Metformin + Nivolumab	USA (IL)	Currently Recruiting

tested for LKB1 mutation), as well as the small overall study population, we only identified one patient with this genetic alteration. This patient had the second-longest OS in the entire cohort, at 45 months, however she was among the youngest patients at 44 years of age and also surprisingly carried an EGFR mutation, which are all likely important contributors to her relatively prolonged survival.

Importantly, the benefits of adding metformin to standard chemotherapy in this population were not hampered by toxicity, as demonstrated in our safety analysis. Indeed, all patients achieved and tolerated the maximum dose of 1000 mg PO BID, save for one patient who died during the dose-escalation phase of trial A due to an unrelated cause. Two grade 4 AEs were recorded, neutropenia and sepsis, which were unlikely related to metformin, as well as one grade 5 AE (colonic perforation) that was attributed to bevacizumab therapy. No new safety signals were identified in this pooled analysis, and our results confirm the previously reported tolerability of metformin use in this setting.

It is important to point out that our primary endpoint, composite PFS, may have been influenced by the differing imaging intervals used in the two trials in this analysis. PFS is inherently affected by the frequency of radiographic evaluation, as asymptomatic progression can often be identified depending on the intervals used. At the very most, this may have led to an overestimation in our estimate of composite PFS. In order to further investigate this, we recalculated composite median PFS under the assumption that each Trial A patient progressed 6 weeks earlier than initially reported, thereby approximating the Trial B imaging protocol. This yielded modified composite PFS estimates of 5.44 months for all patients, 7.21 months for KRAS + patients, and 6.57 months for EGFR + patients. The similarity of these estimates to the originally reported PFS values demonstrates that this effect was present but minimal in our results.

The quality and abundance of preclinical and observational studies demonstrating the anti-neoplastic properties of metformin has led to a growing number of clinical trials evaluating its efficacy in lung cancer. As shown in Table 3, there is considerable interest in studying the use of metformin in earlier stages of disease as well as in combination with other standard treatments, including radiation therapy, TKIs, and now immunotherapy. Accrual to the two trials included in this pooled analysis was unfortunately hindered by rapidly evolving treatment paradigms in NSCLC, especially with regards to checkpoint inhibitor therapy. Nonetheless, this study still represents the largest prospective analysis to date of metformin combined with platinum-based chemotherapy for treatment-naïve, advanced NSCLC. In addition to helping to confirm the previously shown clinical efficacy of metformin in this setting, our study also highlights its promising activity in key molecular subsets for which no effective targeted therapies currently exist. Future efforts should build on this work by prospectively evaluating the efficacy of metformin in populations enriched for these important molecular alterations.

Compliance with ethical standards

Research Involving Human Participants and/or Animals- All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed consent was obtained from all individual participants included in the study.

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Declarations of interest

ABP – none; **KAM** – none; **DJB** – none; **JRB** – Advisory: Amgen, BMS (uncompensated), Genentech, Janssen Oncology, Merck, Syndax; Consulting: Celgene, Eli Lilly; Research Support: BMS, MedImmune/AstraZeneca, Merck; **DSE** – Advisory: AstraZeneca, BeyondSpring, Boehringer Ingelheim, Eli Lilly, Genentech, Guardant; **BPL** – Consulting: AstraZeneca, Celgene, Eli Lilly, Merck, Takeda, Guardant, Genentech; Research Support: Celgene, Boehringer Ingelheim.

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