

Supplementary Online Content

Tsakiridis T, Pond GR, Wright J, et al. Metformin in combination with chemoradiotherapy in locally advanced non–small cell lung cancer: the Ontario Clinical Oncology Group Advanced Lung Cancer Treatment with Metformin and Chemoradiotherapy randomized clinical trial. *JAMA Oncol*. Published online July 29, 2021. doi:10.1001/jamaoncol.2021.2328

eMethods. Detailed Methods

eReferences

eFigure. Distant Progression-Free Survival (DPFS)

eTable. Detailed Survival Outcomes

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Detailed Methods

Exclusion Criteria

Exclusion Criteria included: ECOG performance status > 2; weight loss of > 10% in the past three months; having diabetes or taking metformin or other anti-hyperglycemic therapy; pulmonary function of FEV1 < 1.2 lit/sec or less than 50% of predicted; fasting blood sugar > 7.0 mmol/l; prior systemic chemotherapy for lung cancer, or prior radiotherapy that would overlap with the planned treatment.

Secondary Outcomes for Efficacy

PFS

Time to loco-regional progression was defined from the date of randomization until the date of confirmed loco-regional progression. Patients who died or who had distant metastases without evidence of loco-regional progression were considered as having a competing risk on the day of death/distant progression. Time to loco-regional progression was evaluated using a competing risk analysis.

Distant progression-free survival (DPFS) was defined from the date of randomization until the date of distant progression, or death due to any cause. Deaths were considered an event and not a competing risk as it was hypothesized that any patient deaths in this population without evidence of distant progression likely resulted from unobserved distant progression. Patients with loco-regional progression were followed for distant progression and were not considered a competing risk. Any patients alive, without distant progression, at the time of data analysis, were censored at the last objective evaluation date.

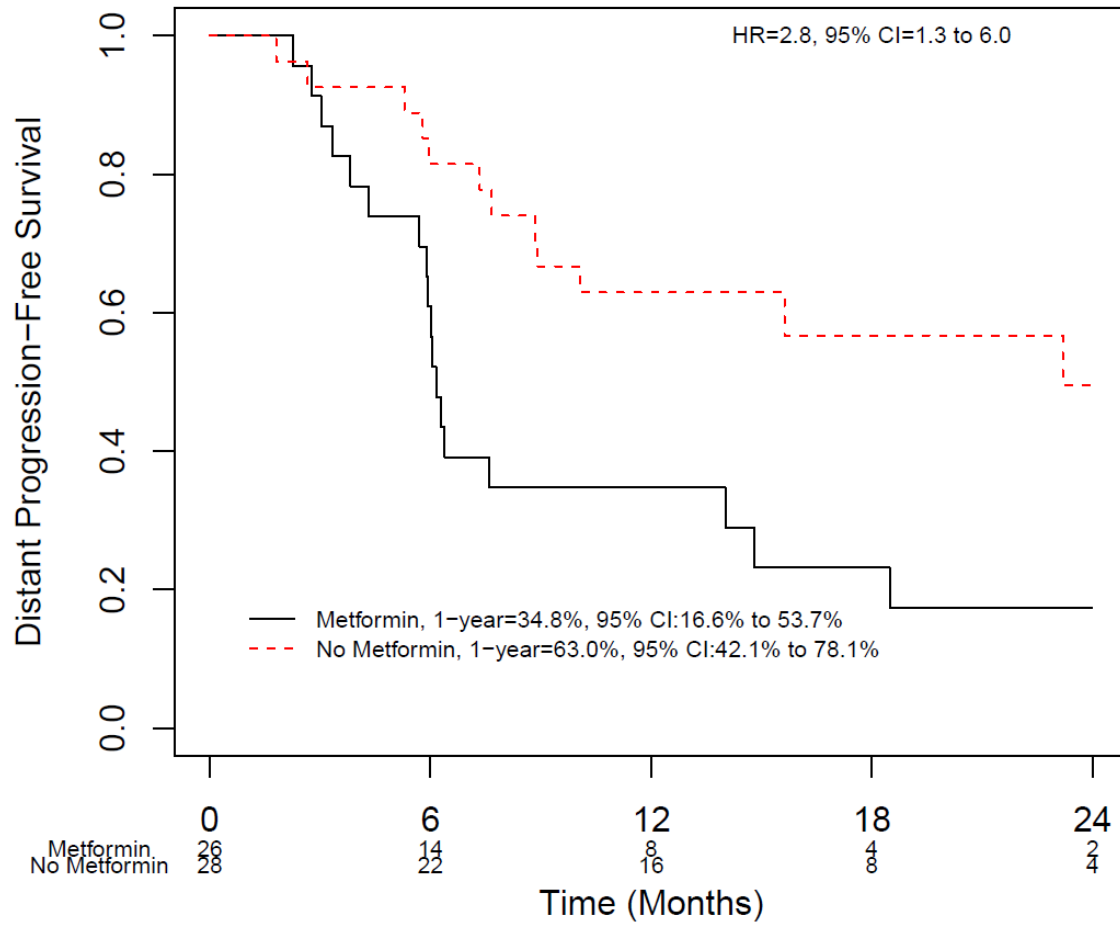
Sample Size

Sample size calculations were based on a 12-month PFS of 45% with chemo-radiotherapy and the postulate that metformin would be of interest for future investigation if it demonstrated a 20% improvement in PFS to 65%. With the outcome defined as a binary variable, using the recommendations of Rubinstein et al.^{1,2} for a screening study design, a one-sided $\alpha=0.20$, a Fisher's Exact Test was determined to have over 80% power to distinguish between 12-month PFS rates of 45% and 65% with 42 patients in each arm (84 patients total). To account for stratification factors and lost to follow up, the total sample size was increased to 94 patients, 47 in each arm. The planned patient recruitment period was 18-24 months.

eReferences

1. Rubinstein L, Crowley J, Ivy P, Leblanc M, Sargent D. Randomized phase II designs. *Clin Cancer Res.* 2009;15(6):1883-1890.
2. Rubinstein LV, Korn EL, Freidlin B, Hunsberger S, Ivy SP, Smith MA. Design issues of randomized phase II trials and a proposal for phase II screening trials. *J Clin Oncol.* 2005;23(28):7199-7206.

eFigure. Distant Progression-Free Survival (DPFS).



eTable: Detailed Survival Outcomes

Outcomes		Metformin (experimental)	Control
Primary Outcome #	Recurrence, Death, or End of Study (i.e. Failure) Prior to 12 Months	18 (69.2)	12 (42.9)
2-sided p-value		0.051	
Progression-Free Survival	N (%) Events up to 2 Years	18 (69.2)	13 (46.4)
	Median (95% CI)	6.0 (5.3, 14.0)	17.3 (8.8, NR)
	6-month (95% CI)	52.2 (30.5, 70.0)	81.5 (61.1, 91.8)
	1-year (95% CI)	34.8 (16.6, 53.7)	63.0 (42.1, 78.1)
	2-year (95% CI)	17.4 (4.7, 36.8)	44.0 (21.8, 64.2)
Cox PH Hazard Ratio (95% CI)		2.42 (1.14, 5.10)	
Cumulative incidence rates for Time to Local Progression	N (%) Events	6 (23.1)	4 (14.3)
	Median (95% CI)	NR	NR
	6-month (95% CI)	17.4 (1.4, 33.3)	3.7 (0, 11.0)
	1-year (95% CI)	21.7 (4.3, 39.2)	3.7 (0, 11.0)
	2-year (95% CI)	27.5 (7.6, 47.5)	20.4 (0.8, 39.9)
Cumulative Incidence Hazard Ratio (95% CI)		2.57 (0.65, 10.07)	
Local Progression-Free Survival	N (%) Events	6 (23.1)	4 (14.3)
	Median (95% CI)	NR	NR
	6-month (95% CI)	17.4 (1.4, 33.3)	3.7 (0, 11.0)
	1-year (95% CI)	21.7 (4.3, 39.2)	3.7 (0, 11.0)
	2-year (95% CI)	27.5 (7.6, 47.5)	20.4 (0.8, 39.9)
Cox PH Hazard Ratio (95% CI)		2.40 (1.14, 5.07)	
Distant Progression-Free Survival	N (%) Events	18 (69.2)	12 (42.9)
	Median (95% CI)	6.2 (5.7, 14.0)	23.2 (8.8, NR)
	6-month (95% CI)	60.9 (38.3, 77.4)	81.5 (65.2, 94.2)
	1-year (95% CI)	34.8 (16.6, 53.7)	63.0 (42.1, 78.1)
	2-year (95% CI)	17.4 (4.7, 36.8)	49.6 (26.8, 68.8)
Cox PH Hazard Ratio (95% CI)		2.78 (1.30, 5.97)	
Overall Survival	N (%) Events	14 (53.9)	7 (25.0)
	Median (95% CI)	10.1 (7.7, NR)	NR
	6-month (95% CI)	82.6 (60.1, 93.1)	96.3 (76.5, 99.5)
	1-year (95% CI)	47.4 (26.3, 65.9)	85.2 (65.2, 94.2)
	2-year (95% CI)	35.6 (16.1, 55.8)	69.5 (45.6, 84.5)
Cox PH Hazard Ratio (95% CI)		3.80 (1.49, 9.73)	

NR = Not reached

Hazard ratio calculated accounting for stratification factors of stage and chemotherapy regimen.