

Metformin in early breast cancer (BC): A prospective, multi-institutional, open-label, neo-adjuvant “window of opportunity” study.

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Background: There is growing pre-clinical, clinical and epidemiological evidence that metformin, being used in Canada for over 50 years, may exert anti-cancer effects through indirect (insulin-mediated) or direct (AMPK/AKT-pathway) mechanisms and it costs about 50¢ Canadian per day. Here, we report final results of a neo-adjuvant “window-of-opportunity” study of metformin in women with operable BC.

Methods: Newly diagnosed, untreated, non-diabetic BC patients received solitary treatment with metformin 500 mg tid after diagnostic core-biopsy until definitive surgery (no other antineoplastic agents). Clinical characteristics [weight, symptoms, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C-30)] and biologic characteristics [insulin, glucose, homeostatic model assessment (HOMA), C-reactive protein (CRP), leptin] were compared pre- and post-metformin as were Terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL, an apoptotic marker) and Ki67 (*our primary end-point*) scored blinded by manual count of positive nuclear-staining. The planned sample-size of 40 patients gave 90% power to detect a 5.5 percentage point change in Ki67.

Results: Thirty-nine patients were enrolled and mean age was 51 years; metformin was given for a median of 18 days, range 13-40 days. Twenty patients had T1 and 19 patients had T2 or T3 tumors; 16 tumors were grade III; 24 were node negative; 32 were ER/PR positive and 5 were HER-2

positive. No major toxicities were encountered - grade 1-2 self-resolving diarrhea, anorexia and abdominal distention occurred in 50%, 41% and 32%. EORTC QLQ scores were stable in all function domains and in overall scores. The main study outcome variables are tabulated below.

Conclusions: Short-term preoperative metformin was well-tolerated and resulted in clinical and cellular effects in keeping with beneficial anti-cancer effects as demonstrated by improved insulin resistance (HOMA), increased apoptosis (TUNEL) and decreased proliferation (ki67).

Variable (units)	Pre-metformin	Mean change	p (Change)
	mean (SD)	(SD)	
Weight (Kg)	70.3 (12.3)	-1.2 (1.4)	<0.0001
BMI (kg/m²)	26.9 (4.6)	-0.5 (0.5)	<0.0001
CRP (mg/L)	2.0 (2.7)	-0.2 (2.6)	0.35
Glucose (mmol/L)	5.30 (0.56)	-0.14 (0.43)	0.045
Insulin (pmol/L)	43.4 (23.9)	-4.7 (18.1)	0.069
HOMA	1.47 (0.95)	-0.21(0.75)	0.047
Leptin (ng/ml)	16.5 (13.0)	-1.3 (7.2)	0.15
TUNEL	0.56 (0.58)	0.49 (1.00)	0.0037
Ki67	36.5(24.8)	-3.0 (9.8)	0.016



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Chair, Selection Committee
Novartis Oncology Young Canadian Investigator Awards

RE: Application by Dr. Saroj Niraula

Dear NOYCIA Selection Committee Chair:

It is with pleasure that I write the strongest possible letter in support of the abstract by Dr. Saroj Niraula entitled "Metformin in Early Breast Cancer: A Prospective, Neo-adjuvant, Open-label 'Window of Opportunity' Study" presented at the American Society of Clinical Oncology Annual Meeting.

Originally from Nepal, Dr. Niraula completed his Medical Oncology training in China and has subsequently spent almost three years obtaining formal training in breast cancer research as a Clinical Research Fellow at the Mount Sinai and Princess Margaret Hospitals in Toronto, Canada. In addition, he is in the process of completing his MSc degree in Clinical Epidemiology at the University of Toronto.

Dr. Niraula has participated as a Clinical Fellow in my Breast Cancer Clinic and has participated in two of my research studies. He is intelligent, energetic and has a great passion for clinical research. He made a major contribution to the study he is reporting and has been involved in all aspects of its design, conduct and analysis. I recommend him highly and without reservation for a Novartis Oncology Young Canadian Investigator Award.

If I can provide any additional information, please feel free to contact me.

Sincerely,

Pamela J Goodwin MD MSc FRCPC
Scientist, Samuel Lunenfeld Research Institute
Marvelle Koffler Chair in Breast Research
and Director, Marvelle Koffler Breast Centre
Professor of Medicine, University of Toronto

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SAROJ NIRLA

I was involved in the reported project starting right from the conception, protocol writing, ethics approval process, trial initiation in all involved sites, recruitment of patients, collection of data, analysis of data and preparation of the abstract along with the upcoming manuscript.

Contribution percentage:

75%