**"Enhancing Outcomes in Medically Inoperable Early-Stage NSCLC with Gut-Targeted Antibiotics and Stereotactic Body Radiotherapy: Results from a Randomized Pilot Study"**

Steven J. Feigenberg1, Francesca Costabile1, Ceylan Tanes2, Kyle Bittinger2, Roderick O'Connor3, Divyansh Agarwal 4, Giorgos Skoufos5, Silvano Salaris6, Artemis Hatzigeorgiou5, Nektarios Kostopoulos1, Shane Lloyd7, Cole Friedes1, Lisha Chen1, Nikhil Yegya-Raman1, Keith Cengel1, William Levin1, Bakir Valentić3, Tyler Quarton10, Alexander A. Shestov3, Abigail Berman8, Jeffrey Bradley1, Amit Maity6, Costantinos Koumenis1, Edgar Ben-Josef1, Andrea Facciabene1,9.

**Abstract:**

*Background:*

Gut microbiota modulation is an emerging strategy to improve cancer therapy outcomes. This study evaluated the safety and therapeutic potential of combining oral vancomycin — a non-absorbed, gut-restricted antibiotic with selective activity against Gram-positive bacteria — with stereotactic body radiotherapy (SBRT) in early-stage non-small cell lung cancer (NSCLC). The underlying hypothesis was that vancomycin-induced changes in gut microbiota could enhance the antitumor effects of SBRT.

*Methods*:

We conducted a randomized, open-label pilot study in patients with early-stage NSCLC. Patients received oral vancomycin (125 mg, four times daily for five weeks, starting one week prior to SBRT). Safety, progression-free survival (PFS), overall survival (OS), gut microbiota composition, gut metabolome, and immune responses were evaluated.

*Results*:

The combination of vancomycin and SBRT was well tolerated, with no Grade 3 or 4 adverse events reported. Vancomycin treatment selectively depleted certain bacterial strains while enriching others, leading to significant restructuring of the gut microbiota and alterations in the gut metabolome, including reductions in short-chain fatty acids (SCFAs) and shifts in other important immunomodulatory metabolites. These changes were associated with dendritic cell and T cell activation, suggesting enhanced systemic immune engagement. Patients receiving vancomycin showed improved outcomes, with a progression-free survival hazard ratio (HR) of 0.42 (95% CI: 0.18–0.96; P=0.049) and overall survival HR of 0.38 (95% CI: 0.14–0.99; P=0.033), compared to controls.

*Conclusions*:

This pilot study demonstrates that gut microbiome modulation using a gram-positive–targeting, gut-restricted antibiotic in combination with SBRT is safe and may improve clinical outcomes in early-stage NSCLC. These findings support further investigation of targeted microbiome modulation strategies as adjuvants to immunogenic therapies like radiation.