

MRI Assessment of a Treatment for Non-Small Cell Lung Cancer in a Mouse Model

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Introduction: Epidermal growth factor receptor (EGFRvIII) mutations results in non-small cell lung cancer (NSCLC)¹. NSCLC represents 80% of all lung cancers and the usual methods of treatments are: surgery, chemotherapy, and radiation. Traceva is a tyrosine kinase inhibitor that shows anti tumor activity, the effectiveness of this inhibitor for the EGFRvIII mutation remains unknown. In this study we used MRI to evaluate the efficacy of Traceva on EGFRvIII induced lung tumors in a NSCLC mouse model.

Method: *Ink4A/Arf*^{-/-} mice and *SPC-rtTA* and *CCSP-rtTA* mice strains were intercrossed to produce experimental cohorts, *Tet-op-EGFRvIII/SPC-rtTA*, *Tet-op-EGFRvIII/CCSP-rtTA* and *Tet-op-EGFRvIII/CCSP-rtTA, Ink4A/Arf*^{-/-} mice. To induce EGFRvIII expression, adult mice (6-week-old) were provided with fresh drinking water containing 2 mg ml⁻¹ doxycycline (Sigma, St Louis, MO) and 5% (w/v) sucrose, whereas controls received a 5% sucrose solution without doxycycline. After continuously giving doxycycline water for 8 weeks, the *Tet-op-EGFRvIII/CCSP-rtTA, Ink4A/Arf*^{-/-} mice were subjected to MRI imaging to determine total tumor burden. The Mice (n = 8) were imaged using a 4.7T animal Bruker MRI system with T2 scans using TR=1018ms, TE= 6.61ms and a fast gradient echo sequence (GEFI) using TR= 230.8ms, TE= 3.3ms with a flip angle = 22.5°, with gating of both Cardiac and Respiration using Biospec Software. For optimal results, respiration was adjusted at a rate of 25-35 breaths per minute with 4-5 cardiac beats per respiratory cycle. After the first MRI, 4 animals with NSCLC volume >100mL were selected for treatment. The mice were treated with 50mg/kg Traceva via gavage daily for a period of 14 days and imaged once a week. The animals were scanned using identical settings and parameters used for the initial MRI.

Results and Discussion: Four animals were selected to monitor drug treatment efficacy during a time course. Animals have responded to Traceva dramatically with an average result of 64% reduction in tumor volume within the first 7 days and 90% reduction within 14 days of daily oral treatment. Figure 1A, and C represent T2 and GEFI scans, respectively, of a subject scanned prior to treatment, where the entire lung is shown to be covered with tumors. Figure 1B and D show the same mouse after 7 days of daily treatment with 50mg/kg of Traceva showing the remaining tumors (white arrows). Figure 1E shows a normal lung for comparison. The animals continued to be treated for an additional 7 days (total 14 days) to determine tumor responses for longer drug exposure. Initial tumor volumes were: 227.7mL, 173.6mL, 755.6mL, and 703.2mL for Subjects 1-4 respectively, while 14 days later their tumor volume was reduced to: 27.2mL, 37.7mL, 46.3mL, and 44.8mL respectively. Tumor volume over a period of time for the four subjects is shown in Figure 2. Using the time course measurements, the trend of the tumors response to the treatment was generated. One can see that the treated tumors decreased exponentially with a regression value of 0.9979. The standard deviation on the first day was high due to the diversity of the initial NSCLC tumor size. Post treatment, the standard deviation was reduced due to Traceva inception. In conclusion Traceva has dramatically reduced the tumor size and number in the lung due to EGFRvIII mutations, following an exponential pattern when continued to be used on a daily basis.

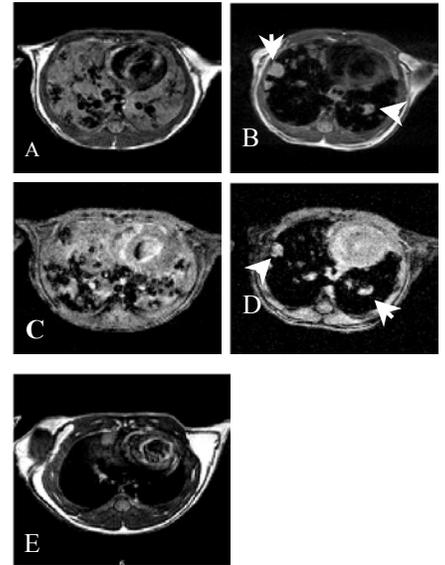


Figure 1: Axial images of a mouse with excessive lung tumors shown in T2 (A) and GEFI (C) while same mouse after 7 days of treatment is shown in T2 (B) and GEFI (D) with arrows showing remaining tumor. (E) T2 axial of a normal mouse.

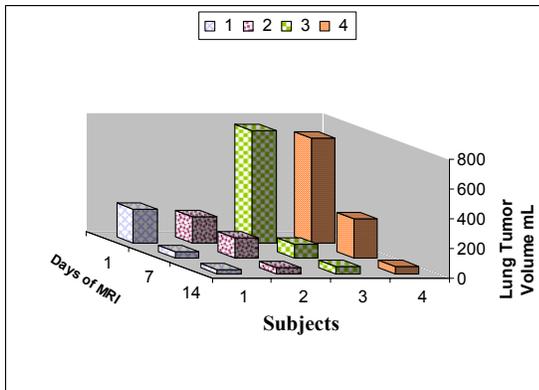


Figure 2: Lung tumor volumes before treatment and after two weeks of daily treatment orally with Traceva for four subjects. Initial tumor volumes are: 227.7mL, 173.6mL, 755.6mL, and 703.2mL for Subjects 1-4 respectively, while 14 days later their tumor volume was: 27.2mL, 37.7mL, 46.3mL, and 44.8mL respectively.

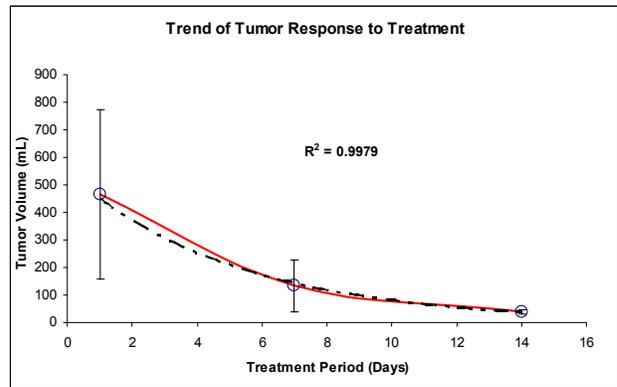


Figure 3: Average tumor response to treatment (red) follow an exponential curve (dashed line) with a regression value of 0.9979.

Reference: Paez, J. G. et al. EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy. *Science* (2004).