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GEFITINIB TREATMENT REVERSES POST-SURGICAL PRO-METASTATIC IMMUNE CHANGES AND IMPROVES SURVIVAL IN A MOUSE MODEL OF OSTEOSARCOMA

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Tweet it! Utilizing gefitinib as an adjunct to primary tumor resection in osteosarcoma mitigates surgery-accelerated metastasis and improves survival in a mouse model. @michelle_kallis #APSA2020

Purpose: Although primary tumor excision can improve survival in osteosarcoma (OS), surgery itself may promote metastatic development. We have found that surgery increases pulmonary metastasis in an OS mouse model, and is associated with pro-metastatic changes in tumor-associated macrophages in the lung. We have also demonstrated that gefitinib, via inhibition of receptor-interacting protein kinase 2 (RIPK2), reduces metastatic burden. In this murine survival study, we examine gefitinib's ability to reverse pro-metastatic immune changes and enhance survival.

Methods: Murine K7M2 OS cells were implanted into the tibia of BALB/c mice. One week following tumor inoculation mice were assigned to 3 groups: 1) tumor-bearing control; 2) amputation of tumor only; 3) amputation with gefitinib. Mice used for immunophenotypic studies (n=10-17/group) were sacrificed 3 weeks following surgery and lungs were isolated for flow cytometric analysis of immune cell populations. Mice used for survival studies (n=15/group) were sacrificed when euthanasia criteria were met.

Results: Comparing the ratio of CD206+ pro-tumor macrophages to MHCII+ anti-tumor macrophages, surgery increased this ratio from 1.6 in tumor-bearing mice to 2.3. Gefitinib treatment was able to reduce this ratio to 1.1 ($p<0.05$). Gefitinib also reduced the presence of the myeloid-derived suppressor cells (MDSCs) within the lung compared to both tumor-bearing and amputated mice (15.0% vs. 23.5% and 24.1%, respectively; $p<0.05$). Median survival of tumor-bearing mice was 39 days compared to 38 days for amputated mice, and amputated mice had greater metastatic burden compared to tumor-bearing mice (54.5% vs 36.6%; $p=0.05$). Gefitinib treatment with primary resection extended median survival to 61 days ($p<0.05$).

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Conclusions: Gefitinib impairs the pro-metastatic immune changes following surgical resection creating a pulmonary microenvironment that is less amenable to metastatic development. Gefitinib treatment increases survival in our murine model.