Combination of Immune Check Points Inhibitors with Conventional Chemotherapeutic Agents in Metastatic Tumor Models

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ABSTRACT

INTRODUCTION AND BACKGROUND: Immunotherapy has revolutionized cancer treatment paradigm with promising approach and strategy for modulating tumor growth and metastatic spread with substantial improvement in patient outcomes. In less than a decade, anti-PD1 therapy has progressed practical therapeutic approach for primary and metastatic tumours. There are research gaps in preclinical evaluation of anti-PD1 antibodies in metastasis and advantage of combining immune check point inhibitors with chemo agents is an upcoming area of preclinical research.

METHODS: In this study we evaluated the preclinical efficacy of mouse PD1 antibody in three experimental lung metastasis models Lewis lung carcinoma (LLC), MCA205 and B16F10 in C57BL/6 mice. The early-stage disease was modelled by intravenous injection of LLC, MCA205, B16F10 cells via tail vein in mice. Three days later disease induction mimics the clinical presence of micro-metastases and treatment was initiated with anti-PD1 10mg/kg,ip;Q4Dx4 doses and standard of care (Cisplatin 5mg/kg,i.v;Q5Dx4 doses or Doxorubicin 4mg/kg,i.v;Q4Dx4 doses). The body weight, clinicals signs, mortality were monitored upto 15-21 days. At the end of the study, lungs were harvested, weighed, perfused with Indian ink, and fixed in formalin for LLC & MCA205 models. For B16F10 model the lungs were perfused and fixed in Bouin's solution for histopathology evaluation.

RESULTS: In MCA205 model, anti-PD1 therapy efficiently abolished and significantly reduced the incidence of no. of metastatic lungs nodules and lung weight compared to vehicle control. In LLC model, anti-PD1 treatment resulted in moderate reduction of no. of metastatic lung nodules. In B16F10 model, the anti-PD1 treatment resulted in marginal metastasis inhibition when compared to standard chemotherapy treatment regimen. Further, histopathological examination of the lung tissues of LLC or MCA205 or B16F10 cells revealed significant number of metastatic pulmonary nodules with clear progressive pattern in vehicle control group. Based on the data, the degree of efficacy ranking for anti-PD1 is MCA205>LLC>B16F10.The exact mechanism of inhibiting pulmonary metastasis in the LCC and MCA205 models remains to be investigated.

RESULTS – *IN VIVO* MONITORING OF ANTI-TUMOR RESPONSE IN MURINE LUNG METASTATIC TUMOR MODELS

Representative images of lung metastasis

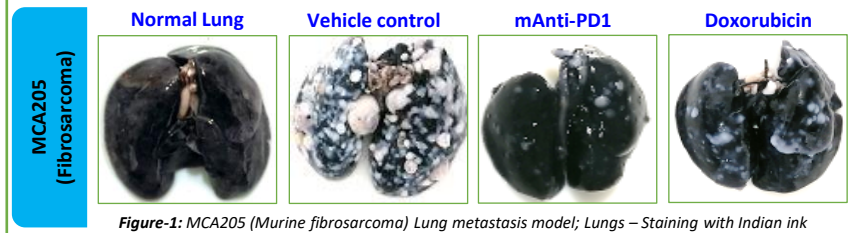


Figure-1: *MCA205 (Murine fibrosarcoma) Lung metastasis model; Lungs – Staining with Indian ink*

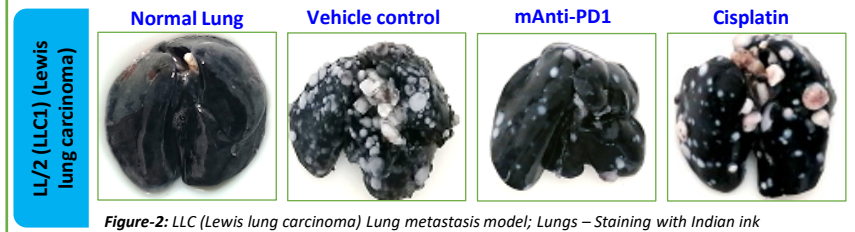


Figure-2: *LLC (Lewis lung carcinoma) Lung metastasis model; Lungs – Staining with Indian ink*

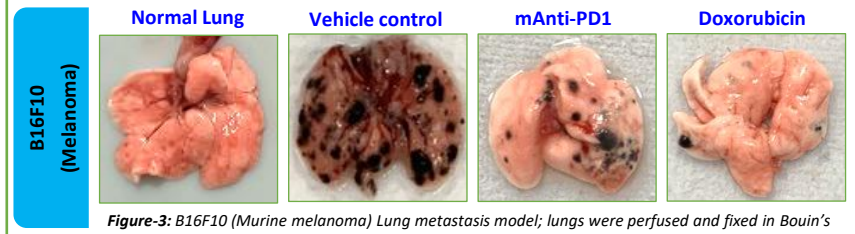


Figure-3: *B16F10 (Murine melanoma) Lung metastasis model; lungs were perfused and fixed in Bouin's solution for count and histopathology evaluation*

Representative images of lung histopathology

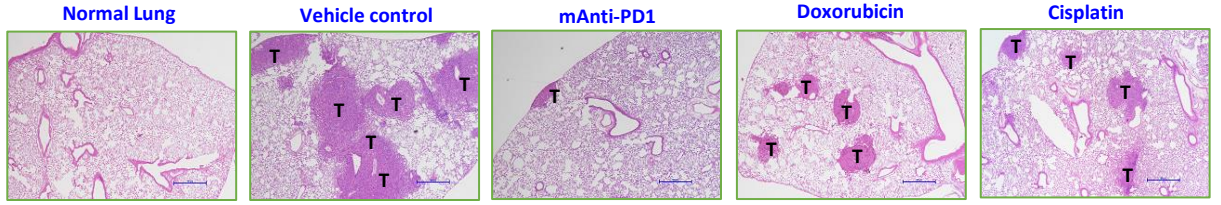
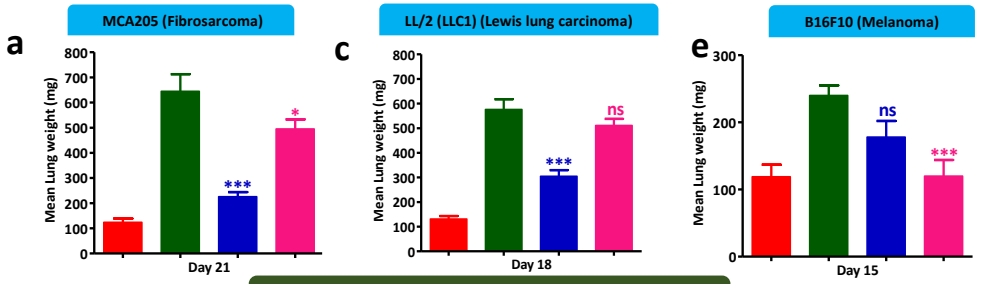
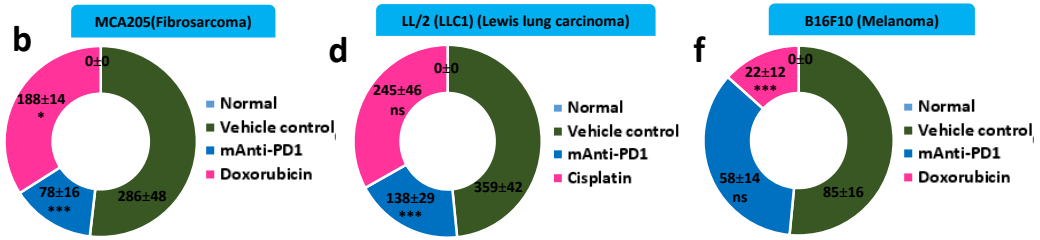


Figure 4: *Histopathology of lung tissues from vehicle control group showed extensive tumor nodules almost occupying the whole lung. The micro metastatic tumours were distributed across all treatment groups. T= Metastatic tumour foci.*

Mean Lung Weight (mg)



Mean No. of Metastatic Nodules



All data is represented as Mean ± SEM n=8-10
(a & b) *In MCA205 metastatic tumor model anti-PD1 treatment group resulted in significantly decreased in Lung weight & no. of metastatic tumor nodules when compared with the Doxorubicin treatment groups* ***(c & d)*** *In LLC tumor model there was mild decreased in Lung weight & no. of metastatic tumor nodules when compared with the Cisplatin treatment groups* ***(e & f)*** *In B16F10 tumor the anti-PD1 treatment resulted in marginal metastasis inhibition when compared to standard Doxorubicin treatment group.* P<0.05, ** p<0.01, *** p<0.001, Statistically significant when treatment groups compared with the respective Vehicle control group.*

CONCLUSIONS

The current data demonstrated the anti-metastatic activity of anti-PD-1 antibody in combination with chemo agents. Further mechanistic studies are required to understand the anti-metastatic efficacy in preclinical models and might pave road for potential clinical evaluation of combination treatment in patients.

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