794 PULSED ELECTRICAL FIELD THERAPY ADDITION TO SYSTEMIC PARADIGMS INCREASES CIRCULATING TUMOR IMMUNITY AND IMPROVES OUTCOMES IN DRUG-RESISTANT MURINE SOLID TUMORS

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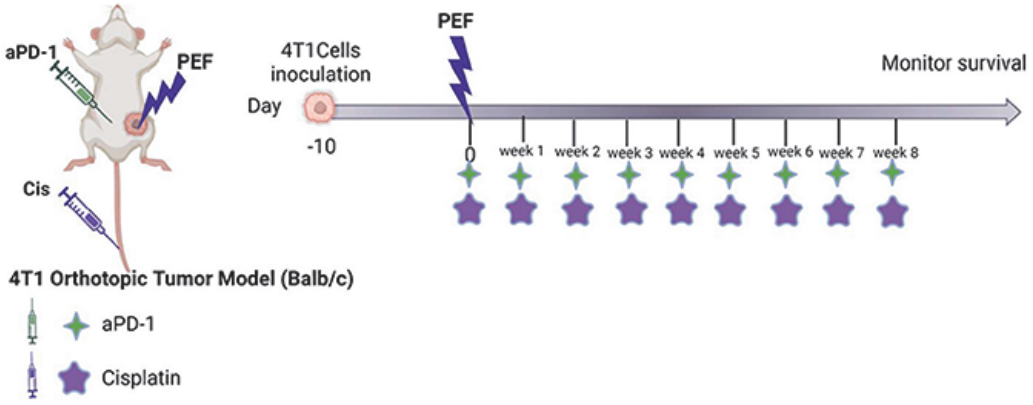
Background Anti-PD1 and systemic chemotherapy, with or without resection, is the standard of care for many tumor types. However, many tumors do not respond to immunotherapy or the combination. Immune 'cold' tumors may become immune 'hot' under the influence of pulsed electric field (PEF) therapy, inducing an adaptive immune response and an abscopal effect. This study determines whether adding PEF to an anti-PD1 and cisplatin regimen improves outcomes in an immune cold tumor model.

Methods Twenty female Balb/c mice were inoculated in the mammary fat pad with 200,000 4T1 cells, a highly aggressive syngeneic orthotopic triple negative breast cancer 4T1 mouse model that is non-responsive to anti-PD1 and only marginally responsive to cisplatin for each treatment group. Once tumors were established (5mm diameter), animals were randomized to systemic-only Cisplatin+anti-PD1 (SOC) or PEF+Cisplatin +anti-PD1 (PEF+SOC) treatment groups. Anti-PD1 (200µg, IP) and Cisplatin (2mg/kg, IV) were administered once weekly for eight weeks, starting on the PEF day (figure 1). Primary tumors were measured three times per week, while overall health, metastases, and survival of the mice was monitored until either death by natural causes or until tumor volume necessitated euthanasia (≥2000mm^3). Flow cytometry on blood collected at day 14 evaluated the systemic immune response.

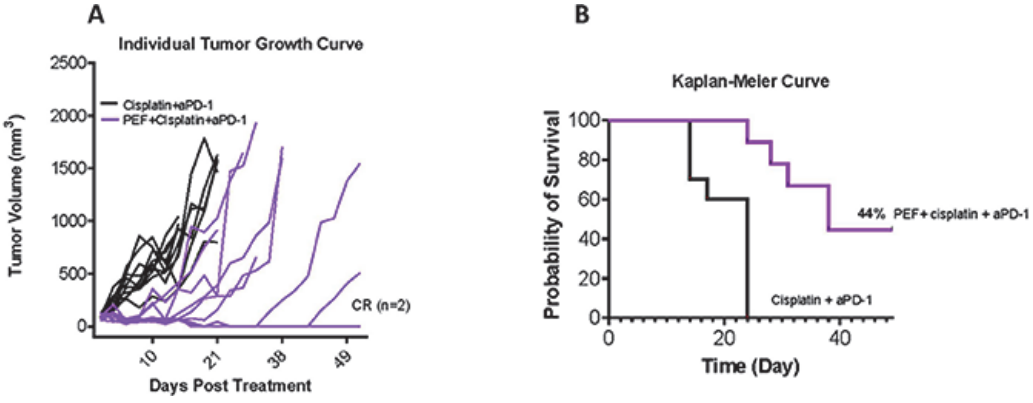
Results The addition of PEF to the systemic therapy resulted in prolonged survival, with 44.4% of the PEF-inclusive group surviving to Day 55, while all mice in the systemic-only therapy group were euthanized by day 24 due to large tumor size (figure 2A,B). The rank-log p-value for the Kaplan-Meier survival curve was statistically significant, P= 0.0002. Circulating immunocyte analysis at day 14 indicated markedly higher CD3, CD4, and CD8 T cells in the PEF-inclusive group versus the systemic-only therapy group, with increases of 3.2x (figure 3A) and significant increase of central memory t cell (figure 3B,C). CD8 T-cells had increased CD69 MFI 'activated' and reduced PD-1 'exhausted' T-cell markers in the PEF-inclusive group versus systemic-only therapy group (figure 4A,B).

Conclusions In a murine model, adding PEF to typical systemic therapy options increases circulating T-cells, with a direct correlation between immunocyte increases and primary tumor response (figure 5A,B). Collectively, our results demonstrate that adding PEF to anti-PD1 and Cisplatin therapy reduces tumor growth, prolongs survival, and activates an adaptive immune response in an immune 'cold' tumor. These results suggest a potential additive benefit to conventional patient care paradigms.

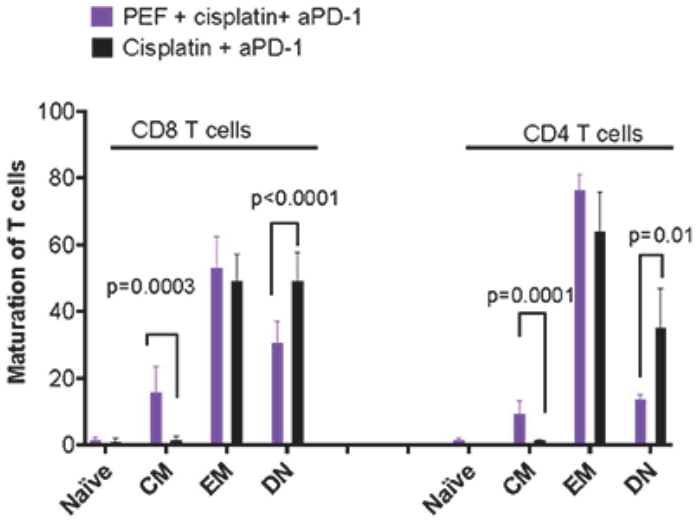
Ethics Approval All animal studies were performed in accordance with the protocols and animal care and use guidelines approved by Institutional Animal Care and Use Committee (IACUC) protocol # 2023–05-01.



Abstract 794 Figure 1 Study designs



Abstract 794 Figure 2 Tumor growth and survival



Abstract 794 Figure 3 Characterization of T-cell immune profiles in 4T1 murine model using flow cytometry

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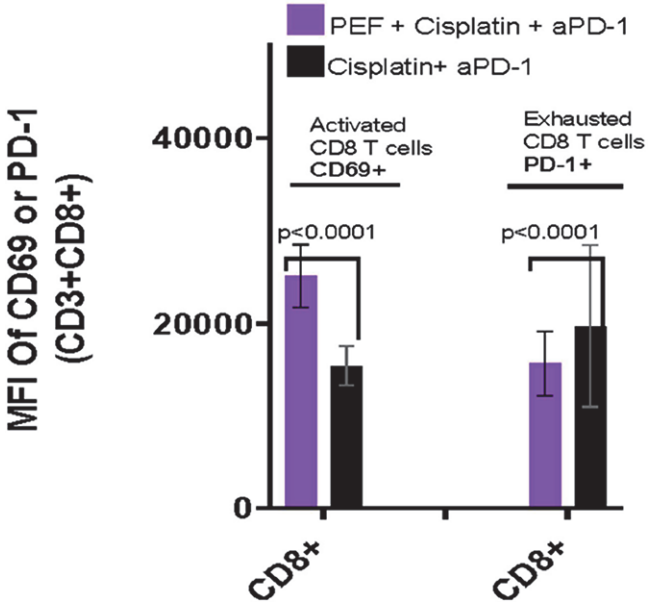
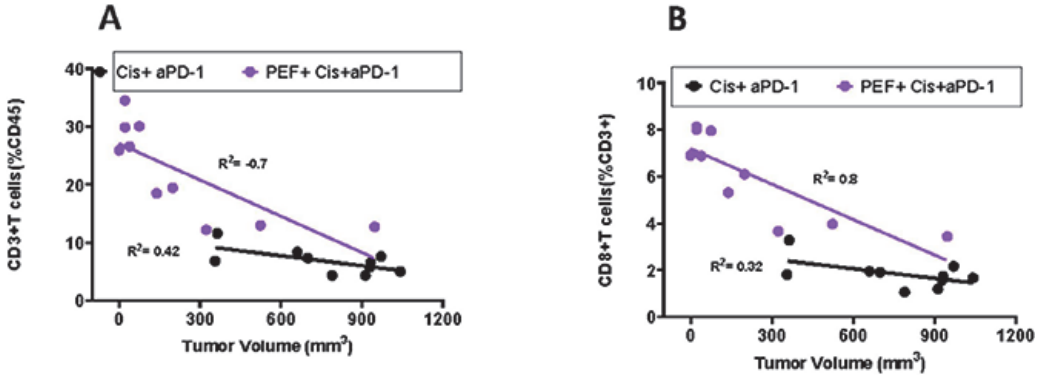


Abstract 794 Figure 4 Activated and exhausted T-cell 4T1 murine model using flow cytometry



Abstract 794 Figure 5 Correlations between tumor size and immune response.