(all races) with stage IV melanomas captured in the NCDB for the periods from 2004–2011 and 2012–2016.

Conclusions Asian patients with melanoma are receiving diagnoses at older ages. Despite decreases in OS for all Asian patients with melanoma, advanced stage IV of the diseases have improved outcomes for the group treated in the era of ICI and TT. Further investigation is warranted to understand the treatment, patient, and tumor characteristics that predict response in this demographic of patients.

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**HISTOTRIPSY FOCUSED ULTRASOUND ABLATION INDUCES IMMUNOLOGICAL CELL DEATH IN TREATED AND DISTANT UNTREATED TUMORS**

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**Background** Histotripsy, a novel image-guided, robotically assisted sonic therapy platform, is a non-invasive and non-thermal tumor ablation modality. We have previously shown that histotripsy potentiates profound innate and adaptive anti-tumor responses in addition to direct tumor destruction. In this study, we sought to characterize the biomarkers of tumor cell death pathways immediately after histotripsy and after the induction of adaptive anti-tumor immune responses in preclinical settings.

**Methods** Immunocompetent C57BL/6 mice were inoculated with bilateral subcutaneous flank injections of Hepa1-6 hepatocellular carcinoma to generate 8–10 mm tumors within 8–11 days. Unilateral subtotal histotripsy was then performed. Mice were euthanized at 6h, and 1, 3, and 10–12 days post-treatment (dpt). Tumors were measured, harvested, fixed, sectioned and studied using multicolor immunohistochemistry.

**Results** Histotripsy decreased treated tumor growth by 50% and abscopal tumor growth by 30–40% compared to untreated tumors at 12dpt, evidencing a systemic anti-tumor immune response that inhibited growth of distant untreated tumor. Treated tumors showed immediate tissue liquefaction in the ablation zone with marked extranuclear translocation of the damage associated molecular pattern HMGB1. At 1dpt, >50% of tumor cells within the ablation zone showed HMGB1 translocation, and 70% of tumor cells at the periphery of the ablation zone showed HMGB1 translocation. Caspase 3 cleavage was not observed in the direct ablation zone, but at the junction of the ablated and non-ablated tissue ~40% cells that released HMGB1 showed cleaved Caspase 3. Caspase 9 cleavage was observed in ~50% cells that had cleaved Caspase 3, suggesting early programed cell death with mitochondrial damage and cytochrome C release 1 dpt; the presence of inflammasome integration/activation suggested pyroptosis induction. Areas of tumor well outside the zone of ablation and within untreated tumors contralateral to ablated tumors did not show early DAMP release or apoptotic cell death compared to the control tumors. However, a robust immune cell infiltration was observed in these locations at 10–12dpt, involving CD8 T-cell infiltration and areas of tumor HMGB1 release in the vicinity of the infiltrating CD8 T cells - indicating the induction of immune rejection of treated and untreated tumors by histotripsy.

**Conclusions** Our results indicate that histotripsy ablation promotes tumor cell death through both immediate mechanical disruption, as well as possible adjacent apoptotic and pyroptotic death. Systemic CD8 T-cell mobilization and immunological cell death in the treated and the contralateral tumors is a novel long term therapeutic benefit.

Reference


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**COSTS OF CARE FOR FIRST-LINE (1L) TREATMENT OF ADVANCED NON-SMALL CELL LUNG CANCER (aNSCLC): A REAL-WORLD CLAIMS ANALYSIS**

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**Background** Recent advances in therapy have created numerous options for the 1L treatment of aNSCLC. This study describes the total direct healthcare costs for patients treated with immunotherapy monotherapy (IO), chemotherapy (CT), or immunotherapy plus chemotherapy (IO+CT) in the 1L setting.

**Methods** The Ability Patient Complete claims database was used to identify US patients aged ≥ 18 years diagnosed with aNSCLC (ICD-9: 162.*; ICD-10: C34.*) initiating 1L treatment with IO, CT, or IO+CT between January 2015 and May 2019. Patients were required to have at least 6 months of continuous enrollment prior to initiation of 1L treatment, ≥ 1 inpatient or 2 outpatient claims for lung cancer, and a claim within 45 days for a secondary metastatic site. Patients with another malignant primary cancer, who participated in a clinical trial, or who received treatments consistent with small cell lung cancer or a systemic therapy not used for lung cancer were excluded. Costs were calculated on a per-patient per month (PPPM) basis from initiation of 1L treatment until discontinuation or end of study period and expressed in 2019 US dollars. A standardized cost approach was applied, with average wholesale prices for antineoplastic and other drug costs and CMS fee schedules for outpatient visits, inpatient stays, ED visits, and other medical costs (e.g. all other outpatient medical services including infusions of growth factors, radiographic studies, blood draws, etc.). All antineoplastic costs were considered individually.

**Results** 8,154 patients were included in the cohort: 1,319 received IO, 5,315 CT, and 1,520 IO+CT. By cohort, mean age was 65 (IO), 63 (CT), and 62 (IO+CT) years while mean Charlson Comorbidity Index was 2.12, 2.11, and 1.83, respectively. Key results by healthcare resource utilization category are provided in the table below (table 1).

**Conclusions** The total PPPM healthcare costs of patients receiving chemotherapy (CT or IO+CT) are higher than those only receiving IO monotherapy. These differences are driven by higher outpatient visit, other medical, and pharmacy costs. IO-containing regimens have higher antineoplastic costs than

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**Regulatory, financial, and access considerations**

Background Chemokines and chemoattractants play critical roles in trafficking that help regulate leukocyte infiltrates in the tumor microenvironment. Chemokines/chemoattractants can also modulate tumor cell phenotype and function, as tumor cells express functional receptors for these agents. Chemerin (retinoic acid receptor responder 2, RARRES2) is an endogenous leukocyte chemoattractant that recruits innate immune cells through its receptor, CMKLR1. RARRES2 is widely expressed in nonhematopoietic tissues and often downregulated across multiple tumor types compared with normal tissue. We and others have shown that augmenting chemerin expression/activity, and concomitantly suppress programmed death ligand-1 (PD-L1) expression compared to controls. Lastly, analyses of clinical trial data from human metastatic prostate cancer patients receiving treatment with ipilimumab (NCT02113657) showed higher tumoral levels of RARRES2 expression correlated with higher levels of PTEN, higher effector immune cell (eg cytotoxic T cells, NK cells) signatures, and improved clinical outcomes, suggesting a strategy to augment chemerin/RARRES2 levels in tumors may improve responses to immunotherapy.

Conclusions Collectively, our data show for the first time that a novel link between chemerin, PTEN, and PD-L1 in human tumor lines. These results show that chemerin – in addition to its ability to suppress tumor growth by recruitment of immune effector cells, may also have a role in improving T-cell-mediated immunotherapies through favorable modulation of PTEN and PD-L1.

Methods We investigated the effect of exogenous chemerin on human prostate and sarcoma tumor lines. Key signaling pathway components were elucidated using qPCR, Western blotting, siRNA knockdown, and specific inhibitors. Functional consequences of chemerin treatment were evaluated using in vitro and in vivo studies.

Results We show for the first time that human tumors exposed to exogenous chemerin significantly upregulate PTEN expression/activity, and concomitantly suppress programmed death ligand-1 (PD-L1) expression. CMKLR1 knockdown abrogated chemerin-induced PTEN and PD-L1 modulation, revealing a novel CMKLR1/PTEN/PD-L1 signaling cascade. Targeted inhibitors suggest that signaling occurs through the PI3K/AKT/mTOR pathway. We found that chemerin treatment significantly reduced tumor migration, while significantly increasing T-cell-mediated cytotoxicity. Chemerin treatment was as effective as both PD-L1 knockdown and the anti–PD-L1 antibody atezolizumab in augmenting T cell mediated tumor lysis. Forced expression of chemerin in human DU145 prostate tumors significantly suppressed in vivo tumor growth, significantly increasing PTEN and decreasing PD-L1 expression. Primary prostate tumor cultures that were treated with recombinant chemerin showed significant increases in PTEN and decreases in PD-L1 expression compared to controls.

Results 1.Comparisons in lg vs. hgPCA: Digital spatial analysis assessing the proximity of CD8+ T-cells to tumor cells revealed a T-cell exclusion phenotype that is more prominent in hgPCA, whereas evaluation of overall CD8+ T-cell density in tumor and stromal regions did not differentiate disease grades. HgPCA had a higher frequency of at least one functional mutation in either TP53, RHPN2, or KMT2D genes CT, but options with no or limited CT may be able to offset these costs through a reduction in other medical expenses.

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Tumor and stromal cell biology

CHEMERIN REACTIVATES PTEN AND SUPPRESSES PD-L1 IN TUMOR CELLS VIA A NOVEL CMKLR1-MEDIATED PATHWAY

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Background Prostate cancer (PCa) is primarily driven by androgen receptor (AR) signaling and has a highly immunosuppressive microenvironment. Although genomic and histopathological differences between low- and high-grade primary PCa (lgPCA and hgPCA) have been reported, an integrative assessment of multiple molecular features in the context of disease grade and metastatic outcome is lacking. We propose that a subset of hgPCA patients who relapse under SOC may benefit from adjuvant immune-checkpoint blockade (ICB) added to SOC to overcome immune suppression.

Methods We analyzed treatment naive prostatectomy tissue from a cohort of 124 primary PCa patients (n= 58, Gleason score ≤6; n= 66, Gleason score ≥8). We performed RNAseq expression profiling, whole-exome sequencing (WES) and immunohistochemistry. We employed digital spatial analysis in tumor vs. stromal regions to characterize differences in CD8+ T-cell topology between lgPCA and hgPCA

Results 1.Comparisons in lg vs. hgPCA: Digital spatial analysis assessing the proximity of CD8+ T-cells to tumor cells revealed a T-cell exclusion phenotype that is more prominent in hgPCA, whereas evaluation of overall CD8+ T-cell density in tumor and stromal regions did not differentiate disease grades. HgPCA had a higher frequency of at least one functional mutation in either TP53, RHPN2, or KMT2D genes

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