Abstract 731 Table 1 Mean PPPM Costs of 1L aNSCLC Treatments

	IO (n=1,319)	IO+CT (n=1,520)	CT (n=5,315)
Total (Medical, Pharmacy, Antineoplastic)	$17,798	$33,819	$19,000
Medical	$2,746	$9,689	$13,178
Inpatient Stays	$697	$718	$772
Emergency Department Visits	$176	$192	$240
Outpatient Visits	$617	$4,239	$2,908
Other Medical Costs	$1,256	$4,540	$9,258
Antineoplastic	$12,153	$20,673	$2,040
Pharmacy (oral non-antineoplastic drugs only)	$2,899	$3,458	$3,782

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

732 CHEMERIN REACTIVATES PTEN AND SUPPRESSES PD-L1 IN TUMOR CELLS VIA A NOVEL CMKRL1-MEDIATED PATHWAY

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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 down-regulated across multiple tumor types compared with normal tissue. We and others have shown that augmenting chemerin in the tumor microenvironment significantly suppresses tumor growth, in part, by immune effector cell recruitment. As chemerin has various roles outside of leukocyte trafficking (eg adipocyte differentiation and metabolic processes), we hypothesized that it may have additional, tumor-intrinsic effects.
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. 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 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.

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733 INTEGRATIVE MOLECULAR PROFILING OF HIGH-GRADE PRIMARY PROSTATE CANCER IDENTIFIES PATIENTS WITH A BIOMARKER PROFILE THAT FAVORS THE COMBINATION OF STANDARD OF CARE (SOC) THERAPY WITH IMMUNOTHERAPY

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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