with partial response and associated with delayed progression (figure 2). CD74 protein was associated with progressive disease during ICI therapy. CSF1R, CD4 and PECAM1 mRNA expression levels in stroma trended with progressive disease.

**Conclusions** In this study we recapitulated the role of OX40L as a marker for response to ICI and CSF1R and PECAM1 in non-response to ICI. 3 CD74 is a receptor for the pro-inflammatory cytokine (MIF) however CD74 ectodomain shedding may function as a decoy receptor. 4 These findings highlight how DSP can be used to probe the tumor microenvironment to identify pathways specific to NSCLC non-response for therapeutic target and biomarker development.

**Ethics Approval** Subjects provided informed consent to Capital Biosciences for genetic and protein analysis.

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**REFERENCES**

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**DEC2 LOSS PROMOTES RESISTANCE OF TUMOR CELLS TO IMMUNOTHERAPY BY AFFECTING CD8+ T CELL-REGULATED TUMOR FERROPTOSIS**

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**Background** Checkpoint blockade therapies have transformed the landscape of cancer care. Durable clinical responses have been observed in a subset of patients. However, many patients do not respond, and understanding the mechanisms that determine tumor resistance to checkpoint blockade drugs could potentially benefit more patients. Ferroptosis is a relatively newly described form of regulated cell death distinct from apoptosis and necroptosis. Recently, T cell-promoted tumor ferroptosis was shown to be an anti-tumor mechanism and targeting this pathway could be a potential therapeutic approach.

**Methods** To identify genes critical to immunotherapy resistance, B16.SIY cells were transduced with a genome-scale gRNA lentivirus to generate loss of function mutants. In vitro primed CD8+ T cells isolated from 2C/Rag2−/− TCR transgenic mice specific for the SIY antigen were co-cultured with transduced B16.SIY tumor cells. Resistant mutants were identified by sequencing the gRNAs of survival clones. The gene encoding Decr2, a peroxisomal 2,4-dienoyl-CoA reductase, was identified. To investigate the role of Decr2 in tumor growth and immune responses in vivo, the Decr2 knock-down or Decr2 overexpressed tumors were transplanted into B6 mice and the mice were subsequently treated with anti-PD-L1 antibody. The tumor microenvironments were analyzed by flow cytometry. To understand the resistance mechanism of Decr2 knock-down tumors, RNA-seq was performed and analyzed. The CD8+ T cell mediated tumor ferroptosis formation in vitro and in vivo was analyzed for lipid reactive oxygen species.

**Results** Decr2 mutants were relatively resistant to CD8+ T cell killing in vitro. Consistent with this resistance to CD8+ T cell killing, Decr2 knock-down tumors showed minimal response to anti-PD-L1 therapy in vivo. RNA-seq analysis of Decr2 knock-down B16.SIY tumors revealed upregulation of ferroptosis-related genes,including slc7a11. Further mechanistic studies showed that Decr2 knock-down tumors displayed defects in ferroptosis in vitro and in vivo.

**Conclusions** Decr2-deficient tumors were relatively resistant to CD8+ T cell killing in vitro and anti-PD-L1 immunotherapy in vivo by modulating CD8+ T cell-induced ferroptosis.

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CLINICAL OUTCOMES OF METASTATIC MELANOMA PATIENTS WITH LIVER METASTASES TREATED WITH ANTI-PD-1 MONOTHERAPY VERSUS COMBINATION IPILIMUMAB/NIVOLUMAB

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Background Recent studies report of liver metastases (LM) as a poor prognostic factor in patients treated with immune checkpoint inhibitors (ICIs),1 but clinical outcomes associated with different ICI regimens remains uncertain. In this study, we investigate melanoma patients with and without LM and assess differential treatment outcomes associated with anti-PD-1 monotherapy and combination ipilimumab/nivolumab (I/N).

Methods We conducted a single-center, retrospective review of advanced stage melanoma patients with and without LM treated with anti-PD-1 monotherapy (nivolumab or pembrolizumab) or I/N between 2012 and 2018. Overall survival (OS) and progression free survival (PFS) were measured from the first dose of treatment to date of death and clinical or radiographic progression, respectively. Univariate and multivariate analysis were performed using Cox proportional hazard (CPH) models and logistic regression models. Inverse probability of treatment weighting using propensity scores in CPH models was used to account for the following baseline covariates: age, ECOG performance status, BRAF status, pre-treatment LDH level, prior therapy status, and number and sites of metastases.

Results 327 patients were identified, 87 with LM and 240 without LM. Patients with LM was associated with worse PFS [HR: 2.1, 95% CI, 1.5 – 3.1] (figure 1) and OS [HR: 3.4, 95% CI, 2.2 – 5.2] (figure 2). Respective 3-year PFS and OS estimates associated with anti-PD-1 monotherapy were 21.8% and 28.7% in patients with LM (figure 3, figure 4); and 36.5% and 57.6% without LM (figure 5, figure 6). Respective 3-year PFS and OS estimates associated with I/N were 46.7% and 56.7% in patients with LM; and 58.0% and 74.4% without LM.

Abstract 241 Figure 2 Forest plot for overall survival in all advanced stage (unresectable or metastatic) melanoma patients treated with anti-PD-1 monotherapy (nivolumab or pembrolizumab) or combination ipilimumab/nivolumab (Ipi/Nivo). n = 327

Abstract 241 Figure 3 Kaplan-Meier curves comparing advanced stage melanoma patients with liver metastases treated with anti-PD-1 monotherapy (nivolumab or pembrolizumab) versus ipilimumab/nivolumab by progression free survival. n = 87

Abstract 241 Figure 1 Forest plot for progression free survival in all advanced stage (unresectable or metastatic) melanoma patients treated with anti-PD-1 monotherapy (nivolumab or pembrolizumab) or combination ipilimumab/nivolumab (Ipi/Nivo). n = 327

Abstract 241 Figure 4 Kaplan-Meier curves comparing advanced stage melanoma patients with liver metastases treated with anti-PD-1 monotherapy (nivolumab or pembrolizumab) versus ipilimumab/nivolumab by overall survival. n = 87


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