LB195 / 8 - AKT degradation selectively inhibits the growth of PI3K/PTEN pathway mutant cancers with wild type KRAS and BRAF by destabilizing Aurora kinase B

April 13, 2022, 9:00 AM - 12:30 PM Section 16

Session LBPO.ET02 - Late-Breaking Research: Experimental and Molecular Therapeutics 2

Jia Xu, PhD, Instructor, Oncological Sciences, The Tisch Cancer Institute at Mount Sinai

Conclusion: Pan-cancer analysis identified that 19% of cases have PI3K/PTEN pathway mutation without RAS pathway mutation, suggesting that these cancer patients could benefit from AKT degrader therapy that leads to loss of AURKB.

LB083 / 8 - BRAF dimer-selective inhibitors synergize with BRAF monomer-selective inhibitors to overcome adaptive resistance and retain therapeutic index

April 11, 2022, 1:30 PM - 5:00 PM, Section 16

Session LBPO.ET01 - Late-Breaking Research: Experimental and Molecular Therapeutics 1 / Chemistry

Poulikos I. Poulikakos. PhD, Associate Professor, Oncological Sciences, The Tisch Cancer Institute at Mount Sinai

Conclusion: Overall, our work supports the notion that for most tumors a "3-drug" combinatorial strategy will potentially be most effective: one drug targeting MAPK signaling directly, such as a MEK inhibitor ("pathway" inhibitor), one drug targeting mutated BRAF or RAS selectively in the tumor ("therapeutic index" inhibitor, e.g. BRAF monomer-selective inhibitor, RAS(G12C) inhibitors, etc.) and one drug targeting components of the feedback loop that is responsible for adaptive resistance ("feedback" inhibitor, e.g. BRAF dimer-selective inhibitors, SHP2 or SOS inhibitors, etc.). Our data contribute to the development of a roadmap for the treatment of MAPK-driven tumors using drug combinations tailored to the specific driver oncoprotein.

3611 - Determining the regulation and role of mreg DC in tumor immunity

April 12, 2022, 2:35 PM - 2:50 PM New Orleans Theater A, Convention Center

Session MS.IM01.01 - Novel Cellular Mechanisms for Immune Evasion in Cancer

Raphael Mattiuz, PhD, Icahn School of Medicine at Mount Sinai

Conclusion: We found that mregDC accumulate within the tertiary lymphoid structures together with activated T cell and B cell programs. We are continuing to generate additional data on mregDC interactions in human tumors tissues that respond or resist PD-1 blockade and should be able to provide additional information at the time of the meeting.

Investigating cancer determinants of tumor immune composition

April 12, 2022, 10:20 AM - 10:38 AM Room 243-245, Convention Center

Session SY19 - Myeloid Cell Control of Therapeutic Antitumor Immunity

Brian Brown. PhD, Professor, Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai

Conclusion: These studies establish Perturb-map for functional genomics within tissue at single cell-resolution with spatial architecture preserved and provide insight into how TGFβ responsiveness of cancer cells can affect the TME (Dhainaut, Rose et al. BioRxiv 2021, doi.org/10.1101/2021.07.13.451021).

1340 / 29 - The role of chemokines CCL8 and CCL12 in diffuse intrinsic pontine gliomas

April 11, 2022, 9:00 AM - 12:30 PM Section 36

Session PO.IM01.01 - Inflammation, Tumor Initiation and Progression

Gonzalo M. Pinero, PhD, Icahn School of Medicine at Mount Sinai

Conclusion: Pharmacological inhibition of CCR1 and CCR5 rendered a reduction in macrophage presence in the tumors, and resulted in an extension of survival in tumor-bearing mice comparable to the effect of standard of care, radiation therapy. Our ongoing experiments aim to elucidate the mechanisms by which CCL8 and CCL12 modulate immune cell infiltration, and determine whether the effect of CCL8/CCL12 loss on survival seen in H3.1^{K27M}-DIPG holds true for H3.3^{K27M}-DIPG-bearing mice.

1517 / 18 - Molecular architecture of replication stress response to oncogene deregulation

April 11, 2022, 1:30 PM - 5:00 PM Section 5

Session PO.MCB07.02 - Genomic Instability 2

David Dominguez-Sola, MD, PhD, Oncological Sciences, The Tisch Cancer Institute at Mount Sinai

Conclusion: We found that *in vivo*, INO80 complex mutations shortened tumor latency in a mouse model of MYC-dependent lymphomagenesis. Collectively, these findings indicate that the replication stress response to oncogene deregulation is unique in its molecular architecture, and modification of this response by partial loss-of-function mutations in cancer facilitates tumor progression.

1634 / 26 - Reduction or loss of *Msh2* confers resistance to temozolomide in glioblastoma

April 11, 2022, 1:30 PM - 5:00 PM Section 11

Session PO.TB01.05 - Cell Line and Animal Models

Gonzalo M. Pinero, PhD, Icahn School of Medicine at Mount Sinai

Conclusion: Our data demonstrate that two weeks of TMZ treatment at a clinically relevant dose of 25 mg/kg provides a significant survival advantage in WT-tumor-bearing mice, while no efficacy was observed in tumor-bearing mice with either heterozygous or homozygous loss of *Msh2*. We are currently evaluating the role of *Msh2* in the efficacy of immune checkpoint inhibitors in glioblastoma.

2922 / 7 - Targeting triple negative breast cancer with a VHL recruiting EZH2 protein degrader

April 12, 2022, 9:00 AM - 12:30 PM Section 40

Session PO.CH02.01 - Structural and Chemical Biology

Brandon Dale, Icahn School of Medicine at Mount Sinai, New York, NY

Conclusion: Here, we characterize MS8815, a VHL-recruiting EZH2 degrader that we created. MS8815 displayed nanomolar efficacy at EZH2 degradation and potent in vitro effects on TNBC cell lines, no off-target interactions and utilized the canonical PROTAC mechanism of action. Based on these promising preliminary results, we report MS8815 as the best-in-class EZH2 PROTAC degrader that is able to efficiently degrade EZH2 and kill TNBC cells.

CT205 / 5 - A phase I/Ib trial of intratumoral Poly-ICLC in resectable malignant pleural mesothelioma

April 12, 2022, 9:00 AM - 12:30 PM Section 34

Session PO.CT01.03 - Phase I Trials in Progress 1

Bailey G. Fitzgerald, MD, Icahn School of Medicine at Mount Sinai

Methods: This is a phase I/Ib study to evaluate the safety of IT poly-ICLC prior to surgical resection for patients with MPM (NCT04525859).

1634 / 26 - Reduction or loss of *Msh2* confers resistance to temozolomide in glioblastoma

April 11, 2022, 1:30 PM - 5:00 PM Section 11

Session PO.TB01.05 - Cell Line and Animal Models

Montserrat Puigdelloses Vallcorba, PhD, Icahn School of Medicine at Mount Sinai

Conclusion: When *PDGFB* was overexpressed in combination with the silencing of *Tp53* to induce tumors, tumor-bearing mice with reduced or deficient *Msh2* demonstrated shorter survival time compared to wild-type tumor-bearing mice. In addition, our results indicate *Msh2* deficiency increases the malignancy of gliomas. Our data demonstrate that two weeks of TMZ treatment at a clinically relevant dose of 25 mg/kg provides a significant survival advantage in WT-tumor-bearing mice, while no efficacy was observed in tumor-bearing mice with either heterozygous or homozygous loss of *Msh2*. We are currently evaluating the role of *Msh2* in the efficacy of immune checkpoint inhibitors in glioblastoma.

4145 / 8 - Novel approach that combines an automated breast cancer grading platform with genomics to personalize risk assessment and management

April 13, 2022, 9:00 AM - 12:30 PM Section 33

Session PO.CL01.02 - Translational Research: Imaging

Michael J. Donovan. MD, PhD, Research Professor of Pathology, Molecular and Cell Based Medicine, Icahn School of Medicine at Mount Sinai

Conclusions: A machine-learning platform outperformed grade and produced accurate recurrence risk models with demonstrated added improvement over clinical and genomic analyses. Future studies include expanded cohort studies to confirm and expand these observations.

Identification of IGF2 as Genomic Driver and Actionable Therapeutic Target in Hepatoblastoma

April 11, 2022, 9:00 AM - 12:30 PM Section 6

Session PO.MCB03.01 - Oncogenes and Tumor Suppressor Genes 1

Jordi Abril-Fornaguera, Icahn School of Medicine at Mount Sinai

Conclusion: *IGF2* is an actionable driver in HB and its overexpression was associated with fetal promoter hypomethylation, LOH or miR483 overexpression. The combination of a mAb against IGF1/2 (xentuzumab) with cisplatin led to remarkable anti-tumoral effects in pre-clinical models, providing the rationale for exploring this regimen in IGF2high HB patients.

5026 - Dynamic changes in circulating protein levels reveal an association between ipilimumab and nivolumab combination treatment with outcomes in squamous cell lung cancer

April 8, 2022, 12:00 PM - 1:00 PM E-Poster Website

Session OPO.BCS01.01 - Bioinformatics and Computational Biology

Edgar Gonzalez-Kozlova, PhD, Associate Professor, Oncological Sciences, The Tisch Cancer Institute at Mount Sinai

Conclusion: Using soluble analyte detection and a data-modeling approach, we identified significant longitudinal changes in 40 serum proteins out of 92 tested in patients with SqCLC treated with nivolumab or nivolumab+ipilimumab. Increases in serum inflammatory markers IL6 and CXCL13 were associated with stable disease or progression. Although overall survival was not statistically different between cohorts, our modeling approaches suggested that IL-8 monitoring may help identify patients benefiting more from the combination vs. nivolumab alone.

Immunogenicity of Poly-ICLC matured dendritic cells as an adjuvant for NY-ESO-1 and Melan-A-MART-1 peptide vaccination compared to Montanide® ISA-51 VG, in study subjects with melanoma in complete clinical remission but at high risk of disease recurrence

April 11, 2022, 9:00 AM - 12:30 PM Section 33, ePoster

Phase II Clinical Trials 1, CT108 / 5 - Session PO.CT02.01

Mansi Saxena, PhD, Associate Facility Director, Vaccine and Cell Therapy Laboratory, The Tisch Cancer Institute at Mount Sinai

Conclusion: This trial reached the primary endpoint of safety and tolerability. Arm B induced a stronger antibody and CD4+ T cell response, especially to NY-ESO-1, whereas the Arm A vaccine appears to be more efficient at eliciting CD8+ T cell responses against MelanA/MART1. The enhanced CD8 T cell response in Arm A versus Arm B, could be attributed to frequency of specific HLA-I alleles in either arms. A deeper investigation into correlation between HLA type and cellular immune response to vaccine is ongoing.

253 / 19 - Analyses of tumor-specific T cell dynamics and tumor immune contexture in microsatellite instability-high cancers in response to first-line therapy

April 10, 2022, 1:30 PM - 5:00 PM Section 12, ePoster

Session PO.TB06.06 - Drug Targeting and Treatment Response of the Microenvironment

Cansu Cimen Bozkus, PhD, Assistant Professor of Medicine Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai

Conclusion: This study will provide insights into the quality and quantity of shared anti-tumor T cells within the periphery and tumor tissues and will help identify the immune correlates of response or resistance to therapy in MSI-H cancer patients.