The WIN Symposium 2024, a landmark event in precision oncology, took place in Abu Dhabi, United Arab Emirates (UAE), on the 1st and 2nd of March 2024; marking a significant collaboration between the Worldwide Innovative Network (WIN) Consortium and Burjeel Holdings. This annual global congress of the WIN Consortium brought together physicians, researchers, and scientists from 30 countries to explore the latest advancements in precision oncology, with the ultimate goal of improving cancer patient care and outcomes worldwide. The call for abstracts attracted 51 submissions with 42 accepted as posters and 3 as oral presentations. This publication features 34 of the accepted abstracts.

The WIN Consortium, a non-profit association headquartered in France, unites 31 world-class academic medical centers, healthcare industries, research organizations, and patient advocacy groups from 18 countries, aligned to launch cancer trials using omic platforms to bolster precision oncology across the world. BMC — Burjeel Medical City, the flagship facility of Burjeel Holdings, is the first member from the UAE and Gulf Cooperation Council countries to join the WIN Consortium. Abu Dhabi was selected as the city to host this year’s congress, marking its inaugural occurrence outside of its traditional place in Europe.

The congress featured a meticulously curated program, including interactive elements that illustrate the principles and best practices of precision cancer treatment including dedicated sessions for precision genomics, precision immunotherapy, precision radiotherapy, precision communityomics, a molecular tumor board, and a precision diagnostics panel. Under the theme ‘Precision and Molecular Oncology: Caring for Patients and Future Generations,’ the congress kicked off with a grand opening featuring 2018 Nobel Laureate, Prof. James Allison, Regental Professor and Chair of the Department of Immunology at the MD Anderson Cancer Center (USA), whose groundbreaking work has revolutionized cancer immunotherapy. He was then joined by leading key opinion leaders and innovators from prestigious institutions such as MD Anderson Cancer Center, Brown University, Weill Cornell Medicine, Mount Sinai, Mayo Clinic, Cleveland Clinic, UC San Diego, University of Calgary, Virginia Commonwealth University, and Sarah Cannon Research Institute and renowned leaders of major precision diagnostic companies such as Guardant Health, Tempus AI, and OncoHelix. Additionally, the platform empowered local physicians and scientists to showcase the UAE’s vision and plans for genomic medicine and precision oncology.

Conference Co-Chairs were Drs Wafik El-Deiry (Chair of WIN Consortium; American Cancer Society Research Professor; Director of Legorreta Cancer Center; Associate Dean of Oncologic Sciences, Warren Alpert Medical School, Brown University, RI, USA), Razelle Kurzrock (Chief Medical Officer & Equal Opportunities and Diversity Officer of WIN Consortium; Professor of Medicine, Associate Director of Clinical Research, Chair of Precision Oncology, MCW Cancer Center and Linda T. and John A. Mellowes Center for Genomic Sciences and Precision Medicine; Founding Director of Michels Rare Cancers Research Laboratories, Froedtert and Medical College of Wisconsin, WI, USA), Humaid Al-Shamsi (Director of Oncology Services, Burjeel Holdings; Professor, Gulf Medical University; President, Emirates Oncology Society, Abu Dhabi, UAE), and Khaled Musallam (Group Chief Research Officer, Burjeel Holdings; Adj. Professor, Khalifa University, Abu Dhabi, UAE).
Abstract #2
Uterine Metastasis from Breast Carcinoma: Two Cases Reports with Literature Review
Amal Chamsi1, Amira Daldoul1, Sonia Zaied1
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Purpose: To highlight rare cases of breast cancer (BC) metastasis to uterus which pose a significant diagnostic and therapeutic challenge. Methods: Two patients treated for uterine Metastasis from BC in the medical oncology department, Fattouma Bourguiba hospital, Monastir, Tunisia between 2015 and 2021. Results: Two postmenopausal patients aged respectively 51 and 42 years old, diagnosed of an infiltrating ductal carcinoma initially classified as stage III luminal B. Both treated by endocrine therapy and had metachronous uterine metastasis after a mean time of 15 months. They did not have any specific gynecologic symptoms. Pathological examination of endometrial curettage specimen and immunohistochemistry findings confirmed diagnosis. The first patient underwent a total abdominal hysterectomy with bilateral salpingo-oophorectomy, and she was not offered systemic chemotherapy (CT), but a close gynecologic follow-up was performed. The evolution was marked by the occurrence of multiple lung and bone metastasis. She died 1 year after the diagnosis of recurrence. The 2nd patient’s metastasis workup before treatment, showed bone progression and peritoneal carcinomatosis. Accordingly, she was referred to the medical oncology department for continued treatment with Paclitaxel CT. Conclusion: Metastatic carcinoma to the uterus from extragenital sites including breast has a grim prognosis. Therefore, a routine gynecological follow-up should be carried out in all BC patients. Therapeutically, surgery is recommended when the disease is restricted to the female genital tract alone with no evidence of recurrence at the site of the primary tumor and axilla and no other distant metastases such as our 1st patient.

Abstract #5 – ORAL PRESENTATION WINNER
Oncobox Platform of RNA Sequencing and Bioinformatic Analysis for Personalized Prescription of Targeted Drugs: Results of Prospective Clinical Trial NCT03724097
Maxim Sorokin1,2,3,11, Andrew Garazha1,2, Maria Suntsova2,3,11, Victor Tkachev1, Elena Poddubskaya5,6, Nurshat Gaifullin5, Tatiana Sushinskaya7, Dmitriy Lantsov8, Vasily Borisov9, David Naskhletashvili10, Kirill Ilavin11, Alexander Seryakov11, Alex Glusker2,3, Alexey Moisseev2,3, Anton Buzdin5,11,12,13*

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Introduction: Interrogating gene expression in tumor can identify up- and downregulated molecular targets of cancer drugs. Here we report the results of prospective clinical investigation NCT03724097 of using RNA sequencing analysis for personalized cancer therapy. Methods: Transcriptomic profiles were analyzed using computational algorithm Oncobox that identifies altered expression of drug target genes and molecular pathways and builds a personalized rating of targeted therapeutics. Oncobox reports were provided to oncologists, and treatment outcomes were assessed. Results: Totally, 239 adult solid cancer patients were enrolled: 135 received cancer drug therapy, others received palliative treatment or radiotherapy, or died before therapy started. Oncobox recommended drugs were prescribed in 59% of the cases receiving therapy. Otherwise, patients received non-targeted therapy or targeted therapy predicted as inefficient by Oncobox (controls). Patients in the Oncobox group were significantly pre-treated compared to controls (mean number of previous lines therapy 2 vs 1.2, respectively), but we observed a longer progression-free survival (PFS) trend in the Oncobox group. Furthermore, post-hoc analysis revealed that time between biopsy collection and tumor molecular profiling significantly impacts Oncobox predictive capacity. Excluding patient cases with biopsy obtained more than 7 months before RNA sequencing led to a statistically significant difference in PFS between Oncobox and control groups with hazard ratio of 0.45 (95% CI: 0.23-0.9, p-value = 0.023). Conclusion: These results suggest that transcriptomic profiling provides clinically relevant therapeutic match and can improve disease control rate in recurrent and/or metastatic solid cancers.
Abstract #5 Figure. Progression free survival (PFS) of patients enrolled in this study. (A) yTNM impact on PFS assessed for patients who received chemotherapy. (B) PFS in Oncobox-guided therapy group (n = 36) vs control group (n = 25). (C) PFS in Oncobox-guided therapy group (n = 21) vs control group (n = 24) after exclusion of patients with old (> 7 months) biopsies from patients treated with targeted drugs between the dates of obtaining biopsy and Oncobox RNAseq. (D) PFS for patients with biopsies collected 7+ months before Oncobox RNAseq (old biopsy) (n = 15) vs patients with biopsies collected less than 7 months before Oncobox RNAseq analysis (fresh biopsy) (n = 21) in Oncobox group.

Abstract #6
Concurrent Early-Stage Colon Cancer and Classic Kaposi Sarcoma with Visceral Lymph Node Involvement: A Case Report
Dima Saleh¹*, Balkis Zaitoun², Maroun El Khoury³, Ahmed Kemmou³
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Kaposi sarcoma (KS) is an angioproliferative tumor that develops subsequent to an infection with the oncogenic human herpesvirus 8. The dissemination and spread of KS exhibit high variability. The disease typically manifests initially on the skin, usually beginning on the lower limbs and then extending to the upper limbs and visceral organs. However, visceral organ involvement in classic KS is rare. We present a case of a 64-year-old HIV-negative male from the United Arab Emirates who presented to the oncology clinic with skin lesions on his back, trunk, and all four limbs persisting for five years. A biopsy confirmed KS, and a staging CT incidentally revealed sigmoid colon thickening with mesocolic lymph node enlargement (Figure). Subsequent colonoscopy with biopsy confirmed a grade 2 moderately differentiated adenocarcinoma invading the muscularis propria. A robotic assisted laparoscopic low anterior resection of the tumor, along with excision biopsy of the enlarged mesenteric lymph nodes, was performed. Pathological analysis of the excised lymph nodes confirmed the absence of lymphatic spread of the adenocarcinoma and paradoxically confirmed the presence of KS, thereby pathologically downstaging the colon tumor to pT2N0. We present a case of the co-occurrence of two primary malignancies with atypical features. Classic Kaposi sarcoma rarely involves visceral organs and is typically confined to the skin. Consequently, the enlarged mesocolic lymph nodes observed on CT were initially thought to be due to metastatic spread from the sigmoid adenocarcinoma, especially given the location and the likelihood of metastasis to the involved lymph node group. However, the histopathological analysis revealed the presence of KS in the enlarged lymph nodes and conferred a lower stage of the colon adenocarcinoma, thereby altering the management approach. Kaposi sarcoma is an angioproliferative tumor with various subtypes. While classic KS usually affects only cutaneous surfaces, suspicion of visceral and lymph node involvement should persist, even in the presence of a co-occurring primary malignancy, such as colon adenocarcinoma in this case.
Abstract #11
Analysis of Thyroid Function Abnormalities in a Group of Patients Treated with Pembrolizumab
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Introduction: Pembrolizumab is an effective anticaner immunotherapy. It is generally well tolerated although immune- related adverse events can occur with thyroid dysfunction being the most common one. An assessment of the clinical and risk factors associated with this dysfunction has not been previously assessed in Iraqi patients. This study aims to evaluate the incidence and risk factors of thyroid function abnormalities related to pembrolizumab immunotherapy. Methods: This is a multicenter prospective study including a total of 100 patients with different cancers who initiated pembrolizumab treatment. Demographic data was collected in addition to the number of treatment cycles, history of thyroid surgery, thyroid disease, chemotherapy, and steroid treatment. Baseline T3, T4 and TSH were measured and assessed periodically. Patients were distributed into 2 groups, those who maintained euthyroid state throughout the course of treatment and the others who developed thyroid dysfunction. The latter was correlated with clinical symptoms or just biochemical alterations without any clinical features (subclinical thyroid dysfunction). Assessment was analyzed looking for any relationship of this dysfunction with age, gender, dose, underlying diagnosis or previous disease or treatment lines.

Results: Thyroid dysfunction (clinical and subclinical) was reported in 31 patients (31%). Female patients were the predominant affected group, 67.74% vs. 30.43% among euthyroid states (p < 0.001). Intriguingly, 38.75% of patients with euthyroidism were ex/current smokers compared with 19.35% of patients with thyroid dysfunction (p < 0.028). The median number of pembrolizumab cycles in patients with euthyroidism and with thyroid dysfunction was 5.0 and 6.5, respectively (p < 0.028). Finally, the presence of thyroid disease was more frequent among patients with thyroid dysfunction than those with euthyroidism (22.58% vs. 4.35%) (p < 0.005). Conclusions: A considerable proportion of patients receiving pembrolizumab can develop thyroid dysfunction. Female gender, number of treatment cycles of pembrolizumab and history of thyroid disease may be risk factors for thyroid dysfunction in those patients.

Abstract #12
Amygdalin’s Anti-Cancer Effects and Toxicity in Breast Cancer Treatment: A Review
Adiba Rakhange1, Suhaila Ahmed2, Fatima Alsaadi3, Mizna Musthafa4, Suhana Riyaz1, Tasneem Sandozi1
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Introduction: Globally, breast cancer constitutes 12.5% of new cancer cases each year. Amygdalin, a cyanogenic glycoside found in fruit kernels like bitter almonds and apricots, is valued for its therapeutic attributes, including antioxidative and antibacterial properties. Recent studies emphasize its anti- tumor effects, involving processes such as apoptosis, toxin release targeting cancer cells, and immunomodulation. However, debates surrounding its efficacy in cancer treatment arise due to concerns about human toxicity. The presence of unverified data emphasizes the importance of investigating amygdalin as a potential avenue for advancing breast cancer treatment. This review examines amygdalin’s anticancer and immunomodulatory effects, and potential toxicity in the context of breast cancer.

Methods: A search was conducted across electronic databases such as Fortune Journals, PubMed, ScienceDirect, and Google Scholar to identify studies on amygdalin’s anticancer effects and toxicity in breast cancer treatment. A thorough review was conducted, analyzing a total of about 20 research papers. Results: Amygdalin can be broken down through enzymatic and acid hydrolysis and converted to hydrocyanic acid—an essential element required to induce apoptosis by down-regulating Bcl-2 protein and up-regulating Bax protein thus inhibiting the proliferation of breast cancer cells. It also induces cell cycle arrest by down regulating MAPK/P53 and nitric oxide, and up regulating the reactive oxygen species. Furthermore, it acts as an immunomodulator by suppressing the expression of many tumor growth signaling molecules and CD4, while up regulating natural killer cells and CD8 expression. However, amygdalin metabolism also produces cyanide ion, which contributes to its toxic effects by causing even non-cancerous cells to undergo hypoxia and lactic acidosis.
**Conclusion:** Despite its potential side effects, amygdalin holds significant promise as a candidate for breast cancer treatment. More investigation is needed to establish the most effective dosage levels, potential combinations with other treatments, and strategies for amplifying its cancer-fighting properties while managing potential drawbacks. Further research is required to better understand the impact of amygdalin, aiming to enhance its potential as a viable therapeutic agent.

**Abstract #13**

**METeoric Response to Capmatinib in Metastatic Lung Adenocarcinoma with MET Exon 14 Skipping Mutation. A Case Report and Literature Review**

Santiago Fontes¹, Megan Berry², Sonia Sanchez³, Marisa Fazzino¹, Juan Pablo Gambini⁵, Diego Kaen⁴

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Non-small cell lung cancer (NSCLC) is a leading cause of death, but over the past decade, there has been tremendous progress in the field with new targeted therapies. The mesenchymal-epithelial transition factor (MET) proto-oncogene has been implicated in multiple solid tumors, including NSCLC. MET dysregulation promoting tumorigenesis is associated with worse outcomes following chemotherapy as compared to non-driver mutated NSCLC and occurs either through mutations causing MET exon 14 skipping (METex14) or gene amplification and overexpression that result in enhanced receptor signaling. Capmatinib is the first FDA-approved targeted therapy for NSCLC with METex14 skipping mutations since 2020. FoundationOne CDx, a comprehensive genomic profiling test for solid tumors, was concurrently approved as a companion diagnostic for capmatinib use. Real-life data of MET exon 14 mutated patients treated with capmatinib outside of a clinical trial are scarce, and there is an urgent need for additional data in the real-world setting, particularly for patients with poorer performance status and for treatment-naïve patients. We report a 72-year-old male patient diagnosed with stage IV lung adenocarcinoma with CNS compromise harboring a METex14 who was treated in the first line with a standard dose of capmatinib. An overwhelming early tumor shrinkage of all lesions was observed and documented after a short period of exposure to targeted systemic therapy and is still maintained, highlighting the activity of this drug in the first line scenario.

**Abstract #13 Figure.** A. PET 18FDG scan which shows multiple hypermetabolic bilateral pulmonary nodules and mediastinal lymphadenopathies. B. Post therapy PET 18FDG scan showing no cervical adenomegalies and reduced radiotracer uptake in pulmonary lesions compared to previous study. C and D. 18FDG PET/CT thoracic axial view, pre (C) and posttherapy (D).

**Abstract #14**

**Circular RNA Profile Identifies circATXN1 is Unregulated and as a Proliferative Factor and Prognostic Marker in Gastric Cancer**

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**Introduction:** Circular RNAs (circRNAs) are a novel class of widespread non-coding RNAs that may regulate gene expression in eukaryotes. The characterization and function of circRNAs in human cancer remain elusive. The aim of this study was to assess the circRNA profile and identify functional and prognostic significance of circRNA in gastric cancer (GC). **Methods:** Ribosomal-depleted RNA sequencing and bioinformatic analysis were performed to identify circRNA candidates. Expression of circRNA was examined in paired normal and cancerous gastric tissues. Molecular and cellular techniques were used to explore the biological function and mechanism of circRNA in GC cells.
The prognostic significance was analyzed by Kaplan-Meier method and Cox proportional hazards model. **Results:** We identified at least 5500 distinct circRNA candidates and a series of circRNAs that are differentially expressed in GC tissues compared with matched normal tissues. We further characterized one circRNA derived from the ATXN1 gene, which was termed circATXN1. The expression of circATXN1 is often upregulated in GC tissues due to the amplification of its genomic locus. circATXN1 may promote cell proliferation by acting as a sponge for members of the miR-15 family. The level of circATXN1 was observed as an independent prognostic marker for overall survival and disease-free survival of patients with GC. **Conclusions:** Our findings suggest that circATXN1 is a novel proliferative factor and prognostic marker in gastric cancer.

**Abstract #18**

**Mechanisms of Enhanced Immunotherapy in Malignant Melanoma: The Synergistic Effects of TMZ and PD-1 Blockade**

Tu Hu1, Jingqin Zhong1, Yu Xu1, Wei Sun1, Yong Chen1

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Malignant melanoma is a challenging malignancy to treat, but combination therapies offer potential improvements in patient outcomes. This study aims to elucidate the underlying mechanisms driving enhanced immunotherapy in malignant melanoma through the combination treatment of temozolomide (TMZ) and programmed cell death protein 1 (PD-1) blockade. Our findings reveal that TMZ treatment induces the upregulation of activating transcription factor 1 (AP1) and activating transcription factor 3 (ATF3), subsequently leading to the increased expression of programmed death ligand 1 (PD-L1). This upregulation of PD-L1 facilitates immune evasion by the tumor, impairing the anti-tumor immune response. Moreover, we uncover that TMZ treatment activates the DNA damage-inducible transcript 3 (DDIT3)-CHAC1 iron death pathway, which promotes T cell sensitization and enhances the immune response against melanoma cells. These mechanistic insights into the synergistic effects of TMZ and PD-1 blockade provide valuable knowledge for the development of effective combination therapies against malignant melanoma. Understanding the intricate interplay between immune evasion mechanisms and T cell sensitization pathways will guide the optimization of therapeutic strategies to overcome treatment challenges and improve patient outcomes.

**Abstract #19**

**Investigation of the Role and Mechanism of a Novel MITF Inhibitor in Reversing BRAF/MEK Inhibitors Resistance in Malignant Melanoma**

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**Introduction:** MITF has long been expected to potentially reverse BRAF/MEK inhibitors (MAPKi) resistance in malignant melanoma (MM) as an undruggable target for small molecules due to the absence of ligand-binding pocket. We previously reported compound TT-012, which specifically destroys the dimer formation and DNA binding activity of MITF, surprisingly showing a strong potent in reversing the MAPKi resistance in MM. **Methods:** A cohort of 160 acral melanoma patients from FUSCC diagnosed between 2008 and 2021 was collected, relevant tumor tissues of which were used to develop tissue chips. Extra 3 precious pairs of MM patients carrying BRAF mutation before and after MAPKi resistance were collected and patient derived xenografts (PDX) were developed afterwards. Besides, several dabrafenib– (BRAFi), trametinib– (MEKi) and combo-resistant cell materials derived from BRAF mutant MM cell lines including A375, SK-MEL-28, WM115 and 1205LU were established. Following RNA-seq and cell derived xenografts (CDX) experiments were done to uncover the underlying mechanism. **Results:** Combining genetic testing and IHC staining of tissue chips, we found an upregulation trend of MITF expression in BRAF mutant group versus BRAF wild type group (p=0.0793). Moreover, the MITF level was significantly increased after MAPKi resistance in all 3 self-control cases. In vitro experiments revealed a down regulation of MITF in MAPKi-persist MM, but a great elevation in MAPKi-resistant cell lines, which was positively related to resistant level and MAPKi treatments. TT-012 was able to decrease MITF in both RNA and protein level and showed a strong potent in reversing MAPKi resistance in vitro and in vivo. PDX-YJ derived from a BRAF mutant MM sensitive to MAPKi showed monotherapy efficacy of TT-012 (p = 0232, 34% reduction),
whereas PDX-YJ-R derived from the same patient’s tumor after MAPKi resistance, showed significant combination drug efficacy of TT-012, dabrafenib and trametinib (P<0.0001, 78% reduction). RNA-seq revealed that the MITF elevation after MAPKi resistance was associated with HDAC1 upregulation. Whether knockdown of HDAC1 or Mocefinostat treatment, a relatively HDAC1 selective inhibitor, could reduce MITF expression and downregulate its downstream pathway. **Conclusions:** MITF expression levels were incrementally increased in BRAF-mutated, mutant, and MAPKi-resistant MM. Here we innovatively introduced TT-012, a MITF dynamic inhibitor, and explored its efficacy and function in reversing MAPKi resistance in MM.

**Abstract #20**

**MITF Inhibition Activates the NF-KB Pathway to Potentiate Antitumor Immunity and Enhance Checkpoint Blockade Efficacy in Melanoma**

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*wsun14@fudan.edu.cn.

Malignant melanoma (MM) is an aggressive skin cancer that poses significant challenges in treatment. Immunotherapy, which harnases the patient’s immune system to suppress tumor growth and spread, has emerged as a promising strategy. However, the clinical response to PD-1 monotherapy in MM remains limited. In this study, we investigated the potential of the MITF inhibitor TT-012 to enhance PD-1 immunotherapy and uncovered its underlying mechanism. Our findings demonstrated that TT-012 prominently improved the efficacy of PD-1 treatment against melanoma cells. Further exploration revealed that TT-012 modulates the expression of the IKBIP gene, thereby influencing the secretion of CCL4, a chemotactic factor that promotes the migration of CD8+ T cells towards melanoma cells. Consequently, the sensitization of PD-1 immunotherapy by TT-012 is mediated through the ikbip-CCL4-CD8+ T cell chemotaxis pathway. Moreover, our study uncovered that TT-012 activates the NF-KB pathway and significantly enhances the expression of PD-L1. Pd-L1, an immune checkpoint molecule, inhibits immune cell activation by binding to PD-1, thereby impairing the effectiveness of immunotherapy. By activating the NF-KB pathway, TT-012 regulates PD-L1 expression, further amplifying the therapeutic efficacy of PD-1 immunotherapy. In summary, our research highlights the potential of the MITF inhibitor TT-012 to sensitize PD-1 immunotherapy and its prospective application in treating malignant melanoma. Additionally, we elucidated the mechanisms by which TT-012 modulates the ikbip-CCL4-CD8+ T cell chemotaxis pathway and the NF-KB-Pd1 pathway. These discoveries provide a novel foundation for the development and optimization of immunotherapy strategies.

**Abstract #21**

**FFPE and Fresh-Frozen Colorectal Cancer Tissue Samples Demonstrate Comparable Capacity in Detection of Cancer Gene Fusion Events by RNA Sequencing**

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**Introduction:** Gene fusion events result in chimeric proteins that are frequently found in human cancers. Specific targeted therapies are available for several types of cancer fusions including receptor tyrosine kinase gene moieties. RNA sequencing (RNAseq) can directly identify fusion transcripts in a single test along with multiple additional biomarkers. However, tumor biosamples are usually formalin-fixed paraffin-embedded (FFPE) tissue blocks where RNA is heavily degraded, which in theory may result in a decreased efficiency of fusion detection. **Methods:** Here we for the first time compared efficacy of
gene fusions detection by RNAseq for matched pairs of freshly frozen in RNA stabilizing solution (FF) and FFPE tumor tissue samples obtained for 29 human colorectal cancer patients, fusion transcripts were detected using specifically designed software. **Results:** We detected no statistically significant difference in number of fusions in FFPE and FF RNAseq profiles and found positive correlation between number of fusions detected and sequencing depth for FFPE data. Known fusion *KANSL1-ARL17A/B* occurred with a high frequency in 69% of the patients. We also found 89 new fusion transcripts not mentioned in literature or listed in ChimerSeq database. Among them, 12 were found in two or more patients, suggesting their possible role in carcinogenesis. In particular, new fusion *MACC1-AC005062.1* was found in 24%, *LEPROT-LEPR* – in 17%, *SMG1-NP/PB13* and *AL353138.1-PTCHD4* – in 14% of the patients. Finally, in one patient we detected a novel potentially clinically actionable in-frame fusion of *LRRFIP2* and *ALK* genes with intact tyrosine kinase domain that can be targeted by ALK inhibitors. **Conclusion:** These results suggest that both FFPE and FF types of cancer tissue biomaterials can be used for detection of fusion transcripts with comparable efficacy in case of sufficient number of RNA sequencing reads.

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**Abstract #22**

**A New Simplified Classification of Cancer Biomarkers**

Muhammad Jawad Hashim*

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Numerous biomarkers have been reported in cancer research studies. These biomarkers are used for cancer diagnosis, estimating survival (prognosis), and for guiding treatment selection (predictive). For example, CA19-9 is a biomarker that can help provide prognostic information for patients with pancreatic cancer. Protein markers (proteomics) can be single molecules or a combination of proteins such as OVA1. Proteomics can be combined with other biomarkers including metabolites and RNA sequences to construct biomarker panels. The metabolic by-products of cancer cells provide a unique signature that reflects their abnormal growth profile, angiogenesis, and apoptosis evasion. Metabolites such as polyunsaturated fatty acids (PUFAs) can be used for diagnostic purposes by comparing with noncancer samples (metabolomics). Genomic markers of malignant disease include (proto)oncogenes, tumor suppressor genes, and DNA repair genes. Integration of genomic biomarkers with proteins, metabolites, and circulating mRNA has led to commercially available kits. Isolating cell-free DNA, mRNA, and noncoding RNA, which are shed by cancer cells into the bloodstream allows ‘liquid biopsy’ using conveniently obtained blood samples. This proliferation of cancer biomarkers has led to information overload, confusion among clinicians, and clinical inertia. Thus, there is a need for a practical classification system. Such a system should serve the needs of clinicians as well as researchers. A new classification is proposed to organize cancer biomarkers (Figure). This classification includes 3 categories: Diagnostic, Prognostic, and Treatment. The term ‘predictive’ was avoided as it may be confused with prognostic. Each category has 5 levels. Levels range from 0 to 4, corresponding to increasing levels of accuracy. Level 0 (zero) corresponds to lack of association or no practical usefulness. Putative biomarkers that are currently under research are designated as Level X. For example, a metabolic marker that is being investigated for use in the diagnosis of colorectal carcinoma can be assigned the classification: DX, PD-L1 expression is a useful marker in triple-negative breast cancer (TNBC) for
therapy with immune checkpoint inhibitors such as pembrolizumab and can be assigned the label: R3. Predictive molecular alterations that can guide treatment choices are the gold standard for cancer biomarkers. By providing a practical classification system for cancer biomarkers (Figure), it is hoped that clinical utilization and research development can be optimized. Clinicians can quickly review the utility and accuracy of biomarkers for each cancer based on this classification.

### Diagnostic Biomarker

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### Treatment Biomarker

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</tr>
<tr>
<td>Weakly influential</td>
<td>R2</td>
</tr>
<tr>
<td>Minimally influential</td>
<td>R1</td>
</tr>
<tr>
<td>No influence on therapy</td>
<td>R0</td>
</tr>
<tr>
<td>Unknown / in research</td>
<td>RX</td>
</tr>
</tbody>
</table>

Abstract #22 Figure. Proposed classification of cancer biomarkers.

### TICTOC: A Phase I/II Study of Tamoxifen and SUBA-Itraconazole Combination Testing in Platinum-Resistant Ovarian Cancer (PROC)

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**Introduction:** Relapsed ovarian cancer patients universally develop chemotherapy resistance (platinum-resistant ovarian cancer [PROC]) with poor prognosis, highlighting a need for novel therapies. Our prior work defined a novel synthetic lethality to treatment with lysosomal drugs in combination with itraconazole in a subset of ovarian cancer cell lines. Highly lysosomotropic tamoxifen is an attractive drug to repurpose, given its use in PROC and low toxicity. The tolerability and efficacy of combination tamoxifen and SUBA-Itraconazole (Lozanoc) was undertaken in this first-in-human clinical trial (NCT05156892). **Methods:** TICTOC is enrolling patients with PROC with a maximum 4 lines of prior therapy. Inclusion criteria included adequate organ function, ECOG 0-1, Glasgow prognostic score < 2 and Khorana score < 3. Part 1 dose escalation employed the rolling-six design of escalating Tamoxifen (20 mg/80 mg daily PO) in combination with SUBA-itraconazole 150 mg BD PO to determine MTD/RP2D of the combination. In addition to standard dose-limiting-toxicity (DLT) criteria, G3+ hypertension lasting > 10 days is considered a DLT. Part 2 cohort expansion will assess the overall response rate (ORR), CA125 response, duration of response, safety / tolerability and pharmacokinetic / pharmacodynamic parameters. The primary endpoint is the incidence, nature, and severity of adverse events. Secondary endpoints include ORR, duration of response, and biomarkers of CA125/RECIST1.1 response. **Results:** Twelve patients (median age 69 y [51–85]) have been treated to date across three dose levels with nine evaluable for toxicity/response. Dose escalation up to tamoxifen 60 mg daily PO is currently recruiting with no DLT events. The combination was tolerable with G1-2 AEs related to SUBA-Itraconazole of fatigue, peripheral oedema nausea and anorexia. There were 4/9 cases of G3 hypertension from SUBA-Itraconazole reversible with antihypertensives. No G3+ AEs from tamoxifen or clot events occurred. Of seven patients with RECIST-measurable disease, (4/7) achieved best response stable disease (Figure) and one patient having a CA125 response. Median PFS was 4.3 (2.9–5.6) months and median OS was 9.8 (9.5–10.1) months. **Conclusion:** The ongoing TICTOC (NCT05156892) trial will inform the tolerability, preliminary efficacy, and biomarkers of response; of combination tamoxifen and SUBA-itraconazole in patients with PROC.
Abstract #24

Swimmers plot of evaluable patients on TICTOC study to date. PR: partial response, SD: stable disease, PD: progressive disease. CA125 response as defined by Gynaecologic Cancer Intergroup (GCIG) criteria.

Abstract #25

New South Wales Early Phase Clinical trials Alliance (NECTA): A Model to Improve Efficacy and Access of Early Phase Clinical Trials for Patients and Sponsors

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**Introduction:** The number and complexity of early phase cancer clinical trials has increased significantly globally over the past decade. Australia is an attractive location for the conduct of first-in-human early phase trials due to efficient start-up timelines, favorable regulatory landscape, and a well-established health system with trained clinical investigators. However, access to clinical trials can be challenging for patients from regional areas, and those with rare biomarkers. To improve the efficiency and access of early phase trials for patients and attract international sponsors, the NSW Early Phase Clinical Trials Alliance (NECTA) was established in 2016. We aimed to document the activities and achievements of NECTA over the past eight years to provide a framework by which clinical research trial centers can cooperate to support the quality of trials, efficacy of patient access and investigator training and expertise. **Methods:** The NECTA network commenced with three large trials units in metropolitan NSW in 2016, which has grown to ten early phase units (including two rural and two regional sites), with a memorandum of understanding between trial sites and the Garvan Institute, and central NECTA manager funded by the Cancer Institute (NSW Government). Three pillars to foster collaboration involving 1) centralized referral pathways, 2) multi-site investigator-
led research, and 3) annual drug-development meeting and fortnightly education podcast with sponsor engagement / funding have fostered the growth of NECTA-facilitated trial activation and enrolment. An investigator-led study utilizing liquid biopsy to facilitate early phase trial selection and enrolment for patients (PANNA-COTA) seeking early phase trials was activated in 2022. **Results:** NECTA’s centralized referral pathway has facilitated ten new enquiries/month from overseas sponsors searching for clinical trial sites, to better align trial portfolios between neighboring trial units to prevent population overlap, and to open trials for patients with rare cancers/biomarkers. NECTA’s fortnightly MDTs have facilitated molecular tumor board discussion of 24 patients seeking Phase 1 trials with liquid biopsy results from the investigator-led PANNA-COTA study. An average of 20 patients (range 14-24) per month have been referred to NECTA utilizing the central phone number and email. The annual drug development meeting held 7 times since 2017, has attracted approximately 2,100 attendees and 77 sponsors to date, resulting in growth in the diversity and quality of biotechnology and pharmaceutical sponsored studies in NSW. Ongoing initiatives includes growth of decentralized trial models utilizing telehealth reviews and increasing social media activity of NECTA with the ongoing ‘Dangerous Ideas in Drug Development’ Podcast. **Conclusion:** A patient-centric early phase trials consortium as modelled by NECTA has the potential to facilitate improvement in patient access to trials, efficiency of trial site selection/start-up and education and training of investigators.

**Abstract #26 – ORAL PRESENTATION WINNER**

**Tertiary Lymphoid Structures Localization and Maturation Heterogeneities Correlate with Divergent Microenvironment Features and Immune Responses of Clear Cell Renal Cell Carcinoma**

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**Introduction:** Tertiary lymphoid structures (TLSs) are organized aggregates of immune cells that form postnatally in non-lymphoid tissues and arise under pathological conditions. The prognostic and predictive value of TLSs in the tumor microenvironment (TME) has increased interest in these structures as potential mediators of antitumor
immunity. However, the clinical implications of the localization and maturation stages of TLSs in clear cell renal cell carcinoma (ccRCC) remain to be elucidated. **Methods:** Immunohistochemistry and multispectral fluorescence were used to evaluate the heterogeneity of TLSs and cell infiltration in the TME. We comprehensively evaluated the prognostic and immunologic implications of TLSs heterogeneity in 625 patients with ccRCC from multiple cohorts. Associations between TLS heterogeneity and immunological activities were assessed by quantification of immune cell infiltration. Spatial transcriptomic data were used in combination with mIF to quantitatively assess the extent of immune cell infiltration. **Results:** TLSs typically comprise B-cell follicles with germinal centers surrounded by T-cell zones and dendritic cells. TLS infiltrates were identified in 34.2% of ccRCC samples, with intratumoral, peritumoral, and both infiltrates in 37.8%, 74.1%, and 11.9% of TLS-positive cases, respectively. A higher proportion of early TLSs was found in peritumoral TLSs ($p = 0.016$), whereas intratumoral TLSs consisted mainly of secondary follicle-like TLSs ($p = 0.004$). Kaplan-Meier analyses showed that the presence of mature TLSs (namely SFL-TLSs with CD23+ germinal centers) was significantly correlated with both better progression-free survival and overall survival. Notably, the presence of TLSs, especially intratumoral TLSs and SFL-TLSs, significantly correlated with better survival and objective response rate in ccRCC patients receiving anti-PD-1/PD-L1 immunotherapies. Interestingly, in ccRCC samples with the presence of peritumoral TLSs enriched with primary follicle-like TLSs, the proportion of tumor-associated macrophages and Treg infiltration in the peritumoral regions increased significantly, showing typical suppressive TME characteristics. Furthermore, spatial transcriptome annotation and multispectral fluorescence revealed that an abundance of mature plasma cells within mature TLSs have the capacity to produce IgA and IgG, which demonstrate significantly higher objective response rates and superior prognosis for ccRCC patients subjected to immunotherapy. A mutually exclusive expression of CXCL9 and SPP1 was observed. **Conclusion:** In conclusion, this study for the first time revealed the implications of TLSs localization and maturation heterogeneity on the immunologic status and responses of ccRCC, allowing the identification of immunophenotypes and the improvement of immune-therapeutic efficacy for ccRCC.
PTV center using the coordinates \((x, y, z)\) obtained from the planning system for measurement. SNC Patient software used for calculating Gamma index (3% 1 mm) and spatial offset between the calculated and measured dose planes. The percentage of difference between TPS calculated and measured point dose were calculated. **Results:** The median gross tumor volume of 23 tumors was 0.344 cm\(^3\) (range 0.056–6.071 cm\(^3\)) and planning tumor volume was 0.852 cm\(^3\) (range 7.159–27.387 cm\(^3\)). The average PTV equivalent diameter was 11.8 mm (7.2–27.4 mm). Gamma results met the TG218 acceptance criteria. The percentage of pixels having gamma < 1 was 96.4 ± 1.53% (range 91.6–100%) and 97.7 ± 1.33 % (range 94.5–100%) without and with spatial shift correction respectively. The mean spatial shift was 0 ± 0.33 mm, 0 ± 0.32 mm, -0.1 ± 0.39 mm in the lateral, longitudinal and vertical direction respectively. The mean deviation of point dose comparison was 0.43 % ± 1.33% (range -2.56 to 2.09%). **Conclusion:** Our results show the dosimetric accuracy of SIMT VMAT Radiosurgery of our Linac. We observed no correlation between the PTV volume with the gamma pass rates and spatial shifts. SRS MapCHECK provides accurate assessment of delivered dose with superior gamma passing results for SIMT.

**Abstract #28**

**Mitochondrial Dynamin-Related Protein-1 as a New Chemo-Sensitizing Target in Resistant Cancer Cells: New Innovative Insights in Cancer Therapy**

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Mitochondrial dynamics have pillar roles in several diseases including cancer. Cancer cell survival is monitored by mitochondria which impacts several cellular functions such as cell metabolism, calcium signaling, and reactive oxygen species (ROS) production. The equilibrium of death and survival rate of mitochondria is important for healthy cellular processes. Whereas inhibition of mitochondrial metabolism and dynamics can have crucial regulatory decision between cell survival and death. The steady rate of physiological flux of both mitochondrial fission and fusion is strongly related to the preservation of cellular bioenergetics. Dysregulation of mitochondrial dynamics including fission and fusion is a critical machinery in cell accompanied with crosstalk in cancer progression and resistance. Many cancer cells express high levels of Dynamin-related protein 1 (Drp1) to induce cancer cell invasion, metastasis and chemoresistance including breast cancer, liver cancer, pancreatic cancer, and colon cancer. Targeting Drp1 by inhibitors such as Midivi-1 helps to enhance the responsiveness of cancer cells towards chemotherapy. The review showed Drp-1 linked processes such as mitochondrial dynamics and relationship with cancer, invasion and chemoresistance along with computational assessing of all publicly available Drp-1
Abstract #28

inhibitors-Drp1-IN-1, Dynole 34-2, Trimethyloctadecylammonium bromide, and Schaftoside showed potential inhibitory effect on Drp-1 as compared to standard Mdivi-1. This emerging approach may have extensive strength in the context of cancer development and chemoresistance and further work is needed to aid in more effective cancer management.

Abstract #29

Public Awareness of Colorectal Cancer Screening in Abu Dhabi, United Arab Emirates, 2024
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Introduction: Colorectal cancer is the most common primary cancer in men and the third most common cancer in women in the UAE. In randomized controlled studies, the benefits of colorectal cancer screening have been demonstrated in terms of decreased incidence and mortality. How compliant the target population is will determine how successful a screening campaign is. The uptake of colorectal cancer screening is influenced by various factors, such as psychosocial factors, provider, and healthcare system characteristics, and sociodemographics. To raise the percentage of people who get screened for colorectal cancer, it is essential to educate the target community about the disease and screening. This study sought to determine the level of public knowledge of colorectal cancer (CRC) screening as well as the obstacles that UAE residents face when trying to get screened for the disease. Methods: A supervised self-administered questionnaire was used in a cross-sectional study carried out in the UAE. The questionnaire included questions regarding the sociodemographic data, attitudes toward screening, and awareness of colorectal cancer. Results: A total of 108 eligible participants from 16 different nationalities and different educational levels in the UAE have completed the survey; 50% (51) belonged to the age group of 30–59 years. 54 (51%) were female, 80 (75%) participants chose blood in the stool as a sign of colorectal cancer, and only 38 (36%) participants chose iron deficiency anemia and fatigue as a sign; 53% of the participants believed that screening started from age 50. Even though 78% of the public knows that
colorectal cancer starts without having any symptoms, only 70% are willing to do a colonoscopy without experiencing any symptoms. However, this increased to 96% when experiencing symptoms and on doctors’ recommendation. Furthermore, of the people who were not willing to do the colonoscopy, 44% of them were discouraged from undergoing colonoscopy for fear of discovering malignant disease, 26% had fear of pain and only 15% said that they would be embarrassed. **Conclusion:** Regardless of the educational level, residents of the UAE were found to have an intermediate general level of CRC knowledge. Introducing novel approaches to increase public awareness of colorectal cancer will facilitate early detection of CRC. To raise knowledge of screening and support early colorectal cancer diagnosis, we advise focused education and screening initiatives.

**Abstract #29 Figure.**

**Abstract #32**
**Artificial Cellular Renewal via Genetic Induction of Secretomes, VSELs and Muse Cells**

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**Introduction:** This study is proposed to explore the possibilities of using a therapeutic treatment of artificial tissue construction via components within the human body through the process of genetically inducing the newly-discovered cells, muse cells and VSELs via the usage of secretomes of the body into utilizing their regenerative properties and capabilities into stimulating the damaged tissue to heal itself with the goal of restoring the original parenchyma and function prior to the sustained damage may it be pathological or traumatic. **Methods:** Secretomes are isolated in cultures, conditioned, then collected via centrifugation for removal of dead cells and finally, concentrated via lyophilization or precipitated by ultrafiltration. Preparation and isolation of VSELs within murine bone marrow and human umbilical cord blood. Both of which are isolated with lysis of RBCs with ammonium chloride followed by staining of TNCs with autoantibodies for CD45 and hematopoietic lineage markers. Muse cells are prepared by isolation from bone marrow, adipose tissue or connective tissue, followed by culturing in media containing growth factor and nutrition, characterized by immunohistochemistry, flow cytometry and gene expression then expanded in culture and finally differentiated into cells of different lineage. **Results:** Studies were conducted involving the usage of secretomes that showed significant findings in stimulating tissue repair and regeneration with examples such as treatment for myocardial infarction, stroke and osteoarthritis. Secretomes were also noted to play a role in neuroprotection, limiting neurodegeneration and even neuroregeneration as seen in a trial conducted for treatment for Alzheimer’s disease and Parkinson’s disease via adipose-derived stem cell secretomes. VSEL clinical trials were most significant for their success when it came treatment of hematological conditions like aplastic anemia in which results from a study conducted on patients who were transfused with purified autologous VSELs showed their safety and efficacy as a treatment of choice. More notably, due to their immunomodulatory properties, VSELs were reviewed for their potential as a method of treatment for autoimmune conditions such as rheumatoid arthritis and multiple sclerosis. **Conclusion:** Muse cells, like their counterparts, possess neurological and regenerative properties that rendered them a candidate for choosing experimental and relatively new methods of treatment. They were also found to have cardiovascular properties in which studies that have been conducted showed their efficiency when it came to treating myocardial infarctions by differentiating into cardiomyocyte-like cells and improve cardiac functions on animal models.

**Abstract #34**
**Artificial Intelligence for the Detection of Acute Myeloid Leukemia from Microscopic Blood Images: A Systematic Review and Meta-Analysis**

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**Introduction:** Leukemia is the eleventh most prevalent type of cancer worldwide, with acute myeloid leukemia (AML) being the most frequent malignant blood malignancy in adults. Microscopic blood tests are the most common methods for identifying leukemia subtypes. An automated optical image-processing system using artificial intelligence (AI) has recently been applied to facilitate clinical decision-making. This study aims to evaluate the performance of all AI-based approaches for the detection and diagnosis of AML.

**Methods:** Medical databases, including PubMed, Web of Science, and Scopus, were searched until December 2023. We used the "metafor" and "metagen" libraries in R to analyze the different models used in the studies. Accuracy and sensitivity were the primary outcome measures.

**Results:** Ten studies were included in our review and meta-analysis, conducted between 2016 and 2023. Most deep-learning models have been utilized, including convolutional neural networks (CNNs). The common and random effects models had accuracies of 1.0000 [0.9999; 1.0001] and 0.9557 [0.9312; 0.9802], respectively. The common effect model and random effects model had high sensitivity values of 1.0000 and 0.8581, respectively, indicating that the machine learning models in this study can accurately detect true-positive leukemia cases. Studies have shown substantial variation in accuracy and sensitivity, as shown by the Q-values and P statistics.

**Conclusion:** Our systematic review and meta-analysis found an overall high accuracy and sensitivity of AI models in correctly identifying true-positive cases of AML. Future research should focus on unifying reporting methods and performance assessment metrics of AI-based diagnostics.

**Abstract #35**

The Accuracy of Artificial Intelligence in the Diagnosis of Soft Tissue Sarcoma: A Systematic Review and Meta-Analysis

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**Abstract #36**

Molecular Profiling of NSCLC Tissues Using Spatial Transcriptomics

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**Introduction:** Lung cancer represents the second most diagnosed cancer worldwide (11.4% of the total cases), and the most diagnosed cancer in men (14.3%) and represents the leading cause of cancer deaths in both men and women (18%). Moreover, the majority of tumors are characterized by dynamic molecular and phenotypic changes that occur in tumor cells which influence therapy resistance and result in poor clinical outcomes. **Methods:** FFPE lung tumor tissue from two lung adenocarcinoma (LUAD) and two lung squamous cell carcinoma (LUSC) patients were evaluated using the 10XGenomics Visium platform. The protocol included sample preparation, preparation of slides, fixing the
Conducted by multicolor flow cytometry. of thymocyte globulin prophylaxis. Gene expression profiling at 1 cells from adult (n=83) and pediatric (n=29) HCT recipients. Methods: system after HCT at the transcriptomic and the cellular level. impact HCT outcomes. Here we present our findings about the important criterion for donor selection and impacts post transplantation (HCT) is a curative therapy for acute immunity-related gene expression was conducted using NanoString Technology. Enumeration of cell subsets was conducted by multicolor flow cytometry.

Results: Unsupervised K-means clustering of the patient population based on the immunity-related gene expression profile separated patients into two clusters namely A and B; with cluster B showing significant upregulation of CD8-T-cell surface markers and signaling molecules (p < 0.05, false discovery rate (FDR)<0.05). Patients belonging to cluster-B were found to have significant odds (p < 0.05) of having CMV serostatus of donor and recipient positive (D+R+). Next, we conducted differential gene expression analysis between patients with CMV D+R+ vs other (CMV D-R-, D+R-, D-R+) at all time points. CMV D+R+ patients showed significant upregulation of cytotoxic T-cell related genes at 3-months post-transplant in adult recipients and at 2-months and 3-months post- transplant in pediatric recipients (Figure). Flow cytometric assessment of cell subsets in both adult and pediatric recipients showed higher CD8-T cells reconstitution over time in CMV D+R+ serostatus patients compared to non-D+R+. Conclusion: CMV serostatus of D+R+ drives the higher CD8-T-cell reconstitution at the transcriptomic and cellular level after HCT. The differential immune recovery pattern influenced by CMV can be an important factor while studying indicators for the prediction of relapse of leukemia post-transplant.

Abstract #38
Cytomegalovirus Serostatus Drives T-Cell Recovery After Stem Cell Transplantation
Amit Kalra, Jeff Hebert, Rehan Faridi, Poonam Dharmani, Meer-Taher Shabani-Rad, Victor Lewis, Jan Storek, Faisal Khan
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Introduction: Allogeneic Hematopoietic Stem cell transplantation (HCT) is a curative therapy for acute leukemias. Cytomegalovirus (CMV) serostatus is an important criterion for donor selection and impacts post HCT outcomes. Here we present our findings about the impact of CMV serostatus on the recovery of the immune system after HCT at the transcriptomic and the cellular level.

Methods: Cryopreserved peripheral blood mononuclear cells from adult (n=83) and pediatric (n=29) HCT recipients at 1-month, 2-month, and 3-month post-transplant were used for the study. All patients were 10/10 human leukocyte antigen (HLA) matched with the donor and received myeloablative conditioning therapy along with anti-thymocyte globulin prophylaxis. Gene expression profiling of 579 immunity-related genes was conducted using NanoString Technology. Enumeration of cell subsets was done using the Illumina platform, FastQC and SpaceRanger were used for primary analysis. Seurat and LoupeBrowser were used for the secondary analysis. Results: Unsupervised clustering revealed six and three clusters in LUAD samples, and six and seven clusters in LUSC samples, based on the transcriptomic profile of the cells in the spots of the capture area. The top 10 upregulated genes in each cluster were identified for each sample. It was noted that differentially expressed genes in clusters include genes encoding hemoglobin, cytokines, histones, and collagens. The inquiry revealed that T cells and B cells markers appear to be more present in LUAD tissue samples than in LUSC tissue samples. Moreover, LUSC tissue samples appear to have cancer associated fibroblasts markers whose expression is spatially variable. Conclusion: given the complex tumor heterogeneity in LUAD and LUSC tissue samples, we were able to observe gene expression in the context of spatial organization lung cancer tumor tissue.

Abstract #39
Early Detection of Acute Graft Versus Host Disease by Assessment of the Immunity-Related Transcriptome
Amit Kalra, Jeff Hebert, Rehan Faridi, Poonam Dharmani, Meer-Taher Shabani-Rad, Jan Storek, Faisal Khan
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Introduction: Graft versus host disease (GvHD) is the most common cause of morbidity and mortality after allogeneic hematopoietic cell transplantation (HCT). Acute GvHD (aGvHD) which typically manifests early after transplant mainly affects the skin, gastrointestinal track, and the liver with different grades of severity. aGvHD grade 2-4 is routinely treated after the development of signs and symptoms resulting in poor response in ~50% of patients. If an early and accurate prediction of ensuing aGvHD is possible, then the high-risk patients can be identified and treated preemptively. Here we present potential immune transcriptome markers that can identify patients at high risk of aGvHD before the signs and symptoms develop.
Abstract #38 Figure. Heat map and PCA plot of the differential gene expression pattern between CMV D+R+ vs other.

Methods: Immunity-related transcriptome profiles at Day 14 post-transplant of patients diagnosed with aGvHD grade 2-4 (n = 13) were compared with patients with no aGVHD (n = 17). Median day of diagnosis of aGvHD gr2-4 was Day 34. All patients received myeloablative conditioning therapy along with anti-thymocyte globulin prophylaxis before transplant. Total RNA was extracted from cryopreserved peripheral blood mononuclear cells at Day 14 post-HCT. Gene expression profiling of 579 immunity-related genes was conducted using NanoString Technology. Results: Patients diagnosed with aGvHD gr2-4 were found to have significantly upregulated expression (Benjamini Hochberg P-value [BHP] < 0.05) of cytotoxic T-cell related surface markers and signaling molecules at Day 14 post-transplant before the occurrence of signs and symptoms of aGvHD. The expression pattern of a panel of 12 significantly upregulated genes namely CD3D (BHP = 0.003), CD3E (0.001), CD8A (< 0.001), CD7 (0.002), STAT4 (< 0.001), LCK (0.001), SH2D1A (0.003), IKZF3 (< 0.001), KLRK1 (0.001), KLRB1 (< 0.001), ZAP70 (< 0.001), CD247 (< 0.001) was used to create a gene score for the prediction of aGvHD. A gene score of > 5 was able to identify patients at high risk of aGvHD gr2-4 with a sensitivity of 92% and specificity of 88%. Conclusion: The immunity related transcriptomic panel of 12 genes identified in this study has the potential to differentiate patients at high risk of aGvHD gr2-4 with high sensitivity and specificity with a technique that can be easily translated into clinical practice. These results can pave the way towards development of preemptive therapy for aGvHD thereby reducing the risk of HCT as a curative therapy for leukemia.

Abstract #40
CD34 Chimerism: An Early Relapse Predictor of Acute Myeloid Leukemia Post-Allogeneic HCT
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Introduction: Allogeneic hematopoietic cell transplantation (HCT) is the only curative treatment for intermediate to high-risk acute myeloid leukemia (AML). However, HCT is associated with significant side effects, for example approximately 1 in 4 recipients experience AML relapse with over 90% of relapse cases being fatal. This mortality rate is closely linked to late detection at a high disease burden stage. Although routine CD13/33 chimerism is the gold standard for measuring engraftment, it has limited sensitivity and specificity to detect relapse at a clinically relevant time, 2–3 months before relapse. In the present investigation, we have assessed if using CD34 chimerism can be a better predictor of post HCT AML relapse.
Methods: Mononuclear cells collected from AML patients post allogeneic HCT were analyzed. DNA was extracted from flow cytometric sorted CD34 cells, amplified using the AmpFlSTR Identifiler Plus kit of 16 Short Tandem Repeat (STR) loci and size fractioned using capillary electrophoresis. Recipient chimerism was calculated using informative markers. Results: CD34 chimerism detected relapse on average 2-3 months prior to impending relapse. Overall, CD34 chimerism had > 85% sensitivity and > 90% specificity at predicting relapse with a 2–3-month lead time to relapse. Conclusion: The utility of CD34 chimerism for detecting AML relapse affords highly sensitive and specific detection with clinically significant lead time. Early detection can allow for prophylactic relapse treatment for high-risk recipients to improve survival and quality of life.

Abstract #41
Somatic Variant Landscape of Acute Myeloid Leukemia Using Targeted Next Generation Sequencing (NGS) Panel: Identification of Clinically Actionable Mutations
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Introduction: Detection of DNA mutations in acute myeloid leukemia (AML) has important implications for disease diagnosis, treatment protocols, disease progression, and more. With the advent of next-generation sequencing (NGS), researchers, clinical scientists, and medical practitioners can gain valuable insight into the molecular nature of different diseases. Targeted DNA sequencing panels are gaining popularity in translational research settings to provide real-time information to guide clinical decision-making. Here, we present the somatic mutation landscape analysis of 545 AMLs sequenced from 2017–2023. Methods: DNA extracted from bone marrow / peripheral blood specimens with high blast count was sequenced using Trusight 54 gene panel on Illumina Miseq Next-generation Sequencing platform. Primary and secondary bioinformatics analysis was performed using Sophia Genetics DDM software. Results: We identified 1899 DNA mutations of clinical significance in 54 pathogenic genes implicated in myeloid malignancies. The top five most common mutated genes included TET2 (27%), ASXL1 (26%), DNMT3A (25%), NPM1 (19%), and RUNX1 (17%). Somatic interaction analysis highlighted several combinations of co-occurring mutations including DNMT3A and NPM1, FLT3 and NPM1, and RUNX1 and SRSF2. We identified classic mutational patterns such as oncogenic hotspots and one-hit knock-out of tumor suppressor genes. Analysis using the Drug Gene Interaction Database identified 16 mutated genes with clinical actionability, which included ASXL1, BCOR, BCORL1, DNMT3A, and FLT3.

Abstract #41 Figure.
Conclusion: NGS Myeloid panel provides an effective platform for comprehensive genomic profiling and identification of mutations with biological and clinical significance in AMLs. Using this targeted sequencing approach in combination with mutational analysis allows cutting-edge technologies to become increasingly available to patients with cancer, which may consequently improve disease survival rates and patient quality of life.

Abstract #42
Deciphering the Intricate Link Between Autophagy and Colorectal Cancer Immune Checkpoints: A Bioinformatics Analysis
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Introduction: The metastatic colorectal cancer (CRC) is associated with poor prognosis, urging the need for novel therapeutic strategies to be investigated. Despite the advances in immunotherapy, there are still obstacles to extending its use beyond the subgroups of patients with CRC with mismatch-repair deficiency (dMMR), with consequently a high tumor mutation burden. Cancer cell's expression of immune checkpoints (ICs) represents a potential indicator of the expected response to immunotherapeutic agents. However, the selection of the valid ICs remains an unsolved query. Autophagy has a variable and contextual role at different stages of cancer; a dynamic effect that can alter tumor growth and cancer response to therapy. The aim is to explore the potential role of autophagy in modulating the expression of different immune checkpoints on the cancer cell surface. Studies on murine melanoma cells and human ovarian cancer suggested that cells overexpressing the programmed death ligand-1 (PD-L1) are more responsive to autophagy inhibitors than cells with weak PD-L1 expression. Our experimental work on HCT116 CRC cell lines knocked out for ATG5 and ATG7, showed a significant increase in tumor mutational burden compared to the parental cells. In addition to PD-L1, Indoleamine 2,3-dioxygenase (IDO), and V-domain Ig suppressor of T-cell activation (VISTA) are other ICs expressed on tumor cells. The current bioinformatics analysis aims to explore the autophagy machinery genes as new biomarkers for response to immunotherapy beyond the classic ones (PD-L1, Tumor mutational burden, and mismatch repair deficiency). Objectives: 1) Investigate the response of ATG5 and/or ATG7 knocked out cell lines to the immunotherapeutic agent targeting PD-1; 2) Study the combined effect of pharmacological inhibitors of autophagy and immunotherapeutic agents in CRC. Methods: Various publicly available CRC patient datasets were used (including TCGA RNA sequence) and analyzed using several bioinformatics web tools to perform in silico analysis. We used Gene Expression Database of Normal and Tumor Tissues 2 (GENT2), Gene Expression Profiling Interactive Analysis2 (GEPIA2), and cBioPortal; to analyze the expression status of different genes in tumor samples, Tumor Immune Estimation Resource (TIMER2); to analyze the tumor-infiltrating immune cells, and UALCAN, to evaluate gene expression and methylation in correlation to survival. Results: The expression of PD-L1 is significantly upregulated in MLH1 and MSH6, but not PMS1 mutant vs wild type cancer (Wilcoxon p-value 0.001 and 0.0006, respectively). VISTA expression is also upregulated in MSH6 mutant cancers (p = 0.007). Our results revealed a significant positive correlation of PD-L1, IDO, and VISTA with different immune cells in the tumor microenvironment. For PD-L1, Spearman Rho 0.6, 0.4, 0.5, 0.8, 0.8, with CD8+, CD4+, Natural killer, myeloid dendritic, M1-macrophages, respectively, p < 0.00001 for all). In comparison, the correlation for IDO (Rho 0.7, 0.3, 0.5, 0.7, 0.9), and in general weaker for VISTA (Rho 0.4, 0.5, 0.4, 0.8, 0.7), with p < 0.00001 for all. There is a positive weak, but significant correlation between the ICs and most autophagy genes (Beclin, LC3B, ATG5, ATG7, ULK1/2, and UVRA). Conclusion: The expression of most autophagy genes is weakly but significantly correlated with the classic ICs that denote potential response to immunotherapy in CRC. If supported by biological validation, autophagy inhibitors may represent a potential adjuvant to immunotherapy.

Abstract #43
Metastatic Poorly Differentiated Adenocarcinoma of the Lung with Marked Elevation of CA-19-9 Level and Negative ALK-1 / PDL 1 Expression
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Introduction: The prognosis of metastatic lung adenocarcinoma is poor. Carbohydrate antigen 19-9 (CA 19-9) is a tumor associated antigen used as a prognostic marker
in pancreatic, colon, and stomach adenocarcinoma. CA 19-9 can be elevated in benign diseases. Few reports addressed the prognostic value of an elevated CA 19-9 in advanced lung adenocarcinoma. We describe a case of adenocarcinoma of the lung with very high CA 19-9 level with negative screening tests for GI and pancreatic cancer. **Case description:** A 39-year-old man presented with 1-week history of fever, left flank pain and progressive dyspnea, dry cough, and weight loss over 6 months. He had history of exposure to pulmonar tuberculosis. Complete blood count, renal and liver function tests were normal apart from elevated alkaline phosphatase 556 IU/L. Imaging investigations revealed left lung consolidation, with bilateral pulmonary nodules, multiple sclerotic lesions in thoracolumbar spine, and multiple bilateral supra and infratentorial brain lesions with edema. The differential diagnosis was Miliary tuberculosis versus metastatic lung cancer. Bronchoscopy showed tumor infiltrating distal end of the left main bronchus. The serum tumor markers revealed high levels of CA 19-9: 24,701.0 units/mL and CA125: 328 units/mL. The acid-fast bacilli smear and TB gene PCR tests were negative. Pathology results of left lung biopsy showed poorly differentiated adenocarcinoma, that was strongly positive for CA 19-9, CK 7 and PDL 1 expression were negative and there was weak TTF-1 staining. Upper endoscopy, colonoscopy, and pancreatic MRI were normal. He was diagnosed with metastatic poorly differentiated adenocarcinoma of lung. He had mutation in KRAS Exon 2 and TP53 Exon 7. He received palliative whole brain radiations (5 fractions, 2 weeks), and oncology team will decide about chemotherapy. **Conclusion:** High CA 19-9 levels have prognostic value in metastatic adenocarcinoma of the lung. Multicenter studies are essential to evaluate this finding.

**Abstract #44**

Unraveling the Interplay of Autophagy and KLF8 in Colorectal Cancer Metastasis: A Bioinformatics Exploration and Insights from Molecular Investigations

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**Introduction:** Colorectal cancer (CRC) is a leading cause of cancer-related deaths globally, emphasizing the need for effective treatments. Autophagy may play role in cancer metastasis through enhancing epithelial-mesenchymal Transition (EMT). Targeting ATG5 and ATG7 (using CRISPR/Cas9) revealed upregulated expression of KLF8, an oncogene associated with EMT induction in cancer cells. Investigating these pathways could offer insights into potential therapeutic strategies for CRC metastasis.

**Methods:** Initially, we utilized qPCR to validate increased KLF8 expression in parental HCT116 cells compared to HCT116 knockout (KO) lines, and in metastatic cell lines LOVO and SKCO1. Additionally, we examined KLF8 expression in an isogenic HCT116 MLH1+/− line alongside its MLH1−/− parental line. Subsequently, bioinformatics analyses were conducted using publicly available datasets (TIMER2, UALCAN, GSCAlite). Subsequent biological assays involved dual inhibition of autophagy via chloroquine (CQ) and KLF8 knockdown using siKLF8, evaluating effects on migration (wound healing assay), invasion (Matrigel assay), and focal adhesion maturation via paxillin and zyxin levels (immunofluorescence staining).

**Results:** In our investigation of KLF8's role in CRC, we utilized publicly available data and web -based tools, revealing a notable correlation between KLF8 and autophagy gene expression in CRC specifically with UVRAG, ULK2 and Beclin1 with Spearman Rho 0.49, 0.44, and 0.5, respectively, with p < 0.00001 for all of the tested autophagy genes. Co-expression analysis with EMT markers consistently showed significant p-values (< 0.00001 for all); specifically, with Zeb1, N-cadherin, and e-cadherin, Spearman Rho correlations of 0.66, 0.47, and 0.54 respectively. KLF8 expression exhibited consistent elevation across various tumor stages and CRC subtypes, particularly heightened in metastatic cell lines LOVO and SKCO1 compared to HCT116. Pharmacological inhibition of autophagy using Chloroquine (CQ) in con junction with KLF8 downregulation significantly reduced CRC cell migration and invasion. Notably, our study explored the modulation of focal adhesion molecules, demonstrating increased zyxin expression upon concurrent autophagy inhibition and KLF8 downregulation, indicative of enhanced mature focal adhesion assembly. **Conclusion:** Our research suggests that targeting both KLF8 and autophagy simultaneously could offer a promising therapeutic strategy for combating metastatic colorectal cancer cells.
Abstract #44 Figure.

Abstract #45
Small Device, Big Impact! A Foray into State-of-the-Art Nanopore Sequencing Technology
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Introduction: Nanopore sequencing is a technique used to determine the sequence and modifications of DNA/RNA nucleotides by measuring changes in electric current as DNA/RNA strands move through a tiny nanopore. This method has been adopted by companies like Oxford Nanopore Technologies, NabSys, and Sequenom and is extensively utilized in various scientific fields such as human genomics, cancer research, metagenomics, and plant sciences. Additionally, its quick processing time, portability, and ability to analyze data in real-time make it promising for applications in healthcare. Methods: The review selected top-quality, relevant, and recent articles, organizing them into sections. It aims to provide a comprehensive look at nanopore sequencing technology, its potential for diagnosing genetic diseases and cancer, monitoring therapy during infections, and future applications. Results: According to the 81 articles we have read, around 26 articles state NT’s application in diagnosis, 25 articles state its monitoring therapy during infections, nine articles state its role in cancer management and 21 articles state its future applications. Using Oxford nanopore technology, a genetic study uncovered a balanced translocation in a patient with developmental retardation, linked to a rare neuro-developmental syndrome known as Shashi-Pena syndrome. RNA sequencing alongside other analyses revealed reduced mRNA expression of ASXL2, suggesting a complex chromosomal rearrangement as the root cause. NT can be used for Viral disease monitoring and has successfully been implemented on-site during viral outbreaks for rapid analysis of viral genome to gain insight into genome evolution and transmission dynamics. ONT also suffices as a powerful tool for studying the composition of various human microbiomes enabling accurate profiling of them. Nanopore sequencing detects rare genetic mutations in real-time, aiding cancer diagnosis and treatment monitoring, including liquid biopsies for early detection. The nanopore sequencing that traced the origin of COVID-19 and at the same time plays a huge future role in the prevention and control of SARS and MERS, which still has not disappeared, also helps in the next global epidemic. Conclusion: Nanopore sequencing, a cutting-edge genetic analysis method, overcomes limitations of earlier methods. It offers single-molecule analysis, longer base readings, real-time sequencing, and direct detection. Despite optimism, there are some challenges for nanopore sequencing which are the high speed of translocation and the low sensitivity. Scientists continue to explore its potential, aiming for breakthroughs in genetic research and diagnostics.

Abstract #45 Figure
Abstract #47
New Hero in Town: AI in Human Genomics and Variant Calling: A Literature Review
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Introduction: Advancements in genomics have revolutionized our understanding of human health and disease. The examination of over 3 billion base pairs in Homo sapiens DNA is a crucial aim of genomic studies. High-throughput technologies, such as next-generation sequencing (NGS), generate vast amounts of genomic data, presenting both opportunities and challenges. Accurate variant calling and mutation detection are essential for personalized medicine, disease diagnosis, and understanding genetic diversity. However, the complexity of genomic data demands innovative approaches. Artificial intelligence (AI), particularly deep learning, has emerged as a powerful tool for extracting meaningful patterns from genomic data. In this literature review, we explore the development and application of AI methods in various aspects of human genomics, assess its accuracy and discuss the potential of using this new methodology to enable genome screening and related services in rural and developing countries, as the current modalities often tax a hefty annual fees, but usage of AI driven modalities severely undercut these in resource expense and hence cost. Methods: We systematically reviewed recent literature (published from 2015 to present) to identify AI tools and models used in human genomics. We assessed the strengths and limitations of deep learning algorithms underlying these genomic tools. Results: Our review highlights the transformative potential of AI in human genomics. Deep learning algorithms have shown remarkable promise in various aspects of human genomics, including variant calling and annotation, disease variant prediction, gene expression regulation, epigenomics, and pharmaco-genomics. AI tools outperform traditional methods, reducing false positives and negatives in variant calling, identifying disease-associated variants with higher precision, and enabling the identification of regulatory elements and potential drug targets. Conclusion: Our review underscores the transformative potential of AI in human genomics. As we move forward, it is crucial to address accessibility and affordability. By leveraging AI and in conjunction with a cheap genome sequencing tool, we can enable genetic screening and diagnostic services for developing nations at a lower cost. Initiatives aimed at democratizing genomics must prioritize equitable access, ensuring that cutting-edge technologies benefit all populations. As we unlock the secrets of our DNA, AI serves as a bridge to a healthier, more inclusive future.

Abstract #48
Copy Number Variation in Donor KIR Genes and Motifs Titrates Natural Killer (NK) Cells
Functional Response to EBV Infections and Influences the Risk of Developing Post-Transplant Lymphoproliferative Disease (PTLD) After Allogeneic HCT
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Introduction: Recipients of allogeneic HCT remain vulnerable to an increased risk of reactivation of otherwise latent viral infections due to an immune compromised state. Uncontrolled reactivation of Epstein-Barr virus (EBV) leading to post-transplant lymphoproliferative disorder (PTLD) is one such major complication after T-cell depleted HCT. Recovering within weeks after transplantation and being first in line of defense against viral infections, natural killer (NK) cells are considered important in the immunopathogenesis of EBV complications. NK cell responses are regulated by activating and inhibitory cell surface receptors, central to which are the killer immunoglobulin-like receptors (KIR). Through these receptors, NK cells discriminate healthy cells from ‘altered’ self-cells by scaling the perturbations in HLA expression after viral transformation of the target cell. Here, we set out to determine whether and how KIR gene and motifs’ content of HCT donors and/or recipients influences the development of PTLD after HCT. Methods: Hypothesizing that diverse NK cell receptor repertoires can titrate NK cell functional responses to EBV infections/reactivation and can potentially modify the risk of developing PTLD, we determined the KIR gene repertoires of 356 HLA-matched donor-recipient pairs of first allo-HCT and 50 healthy donors through Next Generation Sequencing (NGS) of the KIR locus on the Illumina MiSeq platform. PBMCs from KIR typed healthy volunteers were stimulated with EBV-transformed target cells to enumerate NK cell response to EBV as a function of KIR gene content using a multicolor flow cytometry-based assay. Effect of KIR gene profile on development of PTLD
Rare Case of Vasculitis After Long Term Use of Ibrutinib

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Ibrutinib, a Bruton’s tyrosine kinase inhibitor, has revolutionized the treatment landscape for various B-cell malignancies, including chronic lymphocytic leukemia (CLL), and Waldenström’s macroglobulinemia. Although generally well-tolerated, emerging evidence suggests a potential association between ibrutinib and vasculitis. Vasculitis manifestations have diverse clinical presentations including cutaneous lesions, arthralgia, and systemic symptoms. Cutaneous lesions can vary from asymptomatic ecchymosis, petechial rash, to leukocytoclastic vasculitis-like palpable purpura and panniculitis. In most reported cases, the onset of the rash can vary from days to months after initiation of ibrutinib. We present an unusual case of long-term use and cumulative dosages of ibrutinib contributing to the development of vasculitis. A 93-year-old woman with medical history of diabetes mellitus, hypertension, chronic lymphocytic leukemia (2018) started with insidious onset of pain and erythema on her lower extremity. The patient was receiving ibrutinib from 2018-2023. She went to hospital and was given a 10-day course of oral antibiotics for cellulitis. Despite medication, symptoms worsened and she returned to hospital. On physical examination, diffuse reddish purple with bullae and erosive skin lesions that involved all distal extremities, face, ears, and oral mucosa were observed. Initial laboratory showed leukocytosis and altered coagulation panel. Possible diagnoses considered included disseminated intravascular coagulation, vasculitis due to paraneoplastic syndrome, hyper-coagulability syndrome or medication-induced effect. Ibrutinib was discontinued and two units of fresh frozen plasma, cryoprecipitates were given because of DIC suspicion. Laboratory tests for markers of systemic vasculitis (antineutrophil cytoplasm antibodies [ANCA]), antinuclear antibodies, anti DS-DNA, Lupus anticoagulant, antiphospholipid anti-bodies, anticardiolipin antibodies, hepatitis panel, protein C and protein S, anti-thrombin, factor 5 laden, and cryoglobulins were ordered, and all were normal. Punch biopsy of the foot showed hypersensitivity vasculitis. Based on clinical and pathological findings, it was determined that the vasculitis was drug induced. Diagnosing ibrutinib-induced vasculitis poses challenges due to the heterogeneity of clinical presentations and the potential overlap with other possible diagnosis. For ibrutinib, cutaneous adverse events have been reported as one of the most common nonhematologic side effects that occur in 13–27%. The management of ibrutinib-induced vasculitis involves a multidisciplinary approach. Prompt recognition and discontinuation of ibrutinib may be necessary.
Abstract #51
Homologous Recombination Deficiency (HRD) as a Potential Pan-Cancer Biomarker for PARP Inhibition
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Introduction: Targeting HRD with PARP inhibitors is now considered a standard treatment strategy in different tumor types. Whether HRD can be used as a tumor-agnostic predictive biomarker for PARP inhibition is not well established. Methods: A 43-year-old woman with no relevant past medical history or family history of cancer was diagnosed with metastatic uterine leiomyosarcoma with lung metastases in 2020. The patient started first line chemotherapy with doxorubicin achieving a partial response as best response and a duration of response of 5 months. Upon disease progression, the patient was initiated on second line pazopanib but required treatment discontinuation due to treatment-related heart failure with an ejection fraction of 40%. Patient was referred to the phase 1 clinical trials unit at Vall d’Hebron University Hospital. Comprehensive genomic profiling was performed using a CLIA certified panel testing 447 genes. Molecular profiling showed a two-copy deletion of BRCA2. TMB of 4.562 mutations per megabase. Tumor was mismatch-repair proficient. Myriad myChoice HRD Plus showed BRCA2 deletion and a genomic instability score of 69 (threshold 42), supporting HRD. The patient was approached for an early phase clinical trial testing a treatment combination based on a PARP 1/2 inhibitor and temozolomide (TMZ). Results: Treatment was overall well tolerated with no grade 3 or 4 treatment-related toxicities. First CT scan 8 weeks from treatment initiation showed partial response (PR) with tumor shrinkage of the two target lesions located in the liver and mediastinum. Thirteen months after treatment initiation, this patient achieved a RECIST 1.1 complete response (CR) with disappearance of both target lesions, which has been sustained for over 24 months (Figure). Conclusion: The clinical case presented here, supports the potential clinical utility of HRD testing across tumor types.