Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

the start of treatment, the median IgG and lymphocyte numbers were 1150 and 370,5 mg/dL , respectively.The characteristics of the patients are summarized in Table 1. Of the 14 patients, 7 (50%) have any infection and 5/14 (35,7 %) required hospital admission (HA). The most frequent cause of infection was bacterial (35,7 %). 3/14 patients had SARS-COV2 infection, 2 of whom died. The most frequent causes of death were COVID (2/14) and myeloma relapse (2/14). 1/14 (7,14%) patient presented CMV viremia. The summary of side effects is shown in Table 2. **Conclusions:** In our center, the rate of infections is similar to what has been published on these drugs. In a population with a high number of prior lines, BsAbs are safe. The high mortality from COVID is striking. The main limitation of our study is the number of patients.

P-114

Real-world experience with belantamab mafodotin therapy for relapsed/refractory multiple myeloma: a multi-center retrospective study

Tamir Shragai[1], Hila Magen[2], Noa Lavi[3], Moshe Gatt[4], Svetlana Trestman[1], Miri Zektser[5], Chezi Ganzel[6], Osant Jarchowsky[7], Tamar Berger[8], Tamar Tadmor[9], Merav Leiba[10], Katrin Hertzog-Zarfaty[11], Netanel Horowitz[3], Michael Shapira[12], David Varssano[1], Yoav Berger[2], Shahar Frenkel[4], Mark Krauthammer[1], Irit Avivi[13, 14], Efrat Luttwak[1], Yael Cohen[13, 14]

[1]Tel-Aviv Sourasky Medical Center; [2]Sheba Medical Center; [3]Rambam Health Care Campus; [4]Hadassah Medical Center; [5]Soroka University Hospital; [6]Shaare-Zedek medical center; [7]Meir Medical Center; [8]Rabin Medical Center; [9]Bnei-Zion Medical Centert; [10]Assuta Ashdod Medical Center; [11]Shamir medical Center; [12]Assuta Ramat HaChayal Hospital; [13]Tel-Aviv Sourasky (Ichilov) Medical Center; [14]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel

Introduction: Despite the advances in management of multiple myeloma (MM), outcome remains poor for patients who are refractory to drugs from 3 therapeutic classes: proteasome inhibitors, immunomodulators and anti-CD 38 monoclonal antibodies. Belantamab mafodotin (GSK2857916) is a first-in-class anti-BCMA immunoconjugate, showed promising anti-myeloma activity in phase 1 and phase 2 trials, and recently approved for the treatment of advanced RRMM in the US and Europe. **Methods:** This was a retrospective, multi-site study, conducted in 12 hospitals throughout Israel. All consecutive RRMM patients aged 18 years or older who received more than a single dose of belantamab mafodotin as monotherapy or in combination with corticosteroids under GSK expanded access compassionate care, from May 1st 2019 through March 1st 2021, were included. **Results:** One-hundred and six patients included in the study cohort. The overall response rate (ORR) was 45.5% (46/101). Rates of complete response, very good partial response and partial response (PR) were 4.0%, 13.9% and 27.7% respectively. By univariate analysis, no significant association was found between age, sex, triple/penta refractoriness, international staging system and revised inetrnational staging system score, high-risk cytogenetics and extramedullary disease to ORR. The median follow-up was 11.9 (95% confidence interval [CI] 10.0-13.8) months. Median progression-free survival (PFS) was 4.7 (95% CI 3.5-5.9) months for the entire cohort and 8.8 (95%CI 6.6-10.9) months for responders. Median duration of response (DOR) was 8.1 (95% CI 5.7-10.5) months. The median overall survival (OS) was 14.5 (95% CI 9.5-19.6) months. Patients achieving PR or better had a statistically significant longer OS (NR for responders vs. 7.1 for non-responders). At twelve-months the OS was 81.9±6.3% vs 35.0±7.5% in responders vs non-responders (p=0.000016). Safety: Ocular toxicity: Sixty-five patients (68.4%) experienced keratopathy (40% grade 3/4). Blurred vision was reported in 36.8% (6.3% grade 3/4). Four patients (3.8%) discontinued treatment due to ocular toxicity. Non-ocular toxicity: Thrombocytopenia occurred in 27.4% (grade ≥3: 17.9%; one major bleeding) of the patients, anemia in 11.3% (grade ≥3: 3.8%) and neutropenia in 7.5% (grade ≥3 4.7%). Other frequent (≥5%) adverse events were infection (11.3%, grade ≥3: 3.8%) and hypersensitivity/ infusion reaction (7.5%; grade ≥3: 2.8%). Two patients in the entire cohort (1.9%) died of adverse events considered to be related to belantamab mafodotin administration by their treating physicians (both of them infections: pneumonia and sepsis). **Conclusions:** This study presents favorable outcomes in patients with advanced RRMM treated with belantamab mafodotin in a real-world setting. Response rate, duration of response and toxicity profile appear to be comparable to those observed in prospective trial setting. These findings support the role of belantamab mafodotin as valuable treatment option for heavily-pre-treated RRMM patients.

P-115

Unc-51 Like Kinase 3 protein (ULK3)-mediated autophagy is responsible for multiple myeloma resistance to chemotherapy

Marilena Tauro[1], Tao Li[1], Mark Meads[1], Praneeth Sudalagunta[1], Raghunandan Reddy Alugubelli[1], Nicholas Lawrence[1], Ernst Schonbrunn[1], Harshani Lawrence[1], Kenneth Shain[1], Conor Lynch[1]

[1]H Lee Moffitt Cancer Center

Introduction: Multiple myeloma (MM) is an incurable disease. Classical chemotherapeutics including bortezomib, melphalan, lenalidomide and thalidomide have greatly enhanced survival times. Unfortunately, patients typically relapse and become refractory with an average survival of 5-6 years post-diagnosis. Our emerging studies demonstrate a novel role for ULK3 in regulating autophagy in MM, a key program that sustains cell survival under times of stress and has been implicated as a major mechanism of proteasome inhibitor (PI) resistance. MM is known to be highly dependent on autophagy and, currently, specific ULK3 inhibitors are lacking. We posit that by targeting this marker in chemotherapy resistant MM patients, we can circumvent alternative metabolic routes and re-sensitize to standard of care pro-apoptotic therapy. **Methods:** We performed RNASeq analysis of CD138+ MM cells derived from patients across

the disease stages spectrum (n=815) to confirm the role of ULK3 in disease progression and resistance to chemotherapy. We developed novel inhibitors SG3014/MA9060 that target multiple kinases including ULK3 (EC50 90nM) as well as BRD4. BRD4 is a known driver of MYC and its expression is increased in refractory MM. The BRD4 inhibitor, JQ1, effectively impairs the tumorigenic potential of MM but resistance has also been noted. We determined the efficacy of MA9060 for the treatment of CD138+ MM isolated from naïve and refractory patients using a novel ex vivo high throughput platform developed at Moffitt. **Results:** ULK3 is highly associated with MM stage of the disease. Refractory MM patients have increased autophagy activity with significantly higher expression of ULK3 in refractory patients and in drug resistant cell lines (immunoblotting U266 vs U266-PSR; RPMI-8226 vs RPMI-8226-B25; ABNL vs V10 resistant cells). Genetic ablation of ULK3 by siRNA in U266 and 8226 cell lines results in rapid cessation of the downstream autophagy proteins (ULK1, ATG13, pATG13) and MM cell death within 72h of transduction. Increased concentrations of autophagy inhibitors MA9060/SG3014 progressively decreased CMYC and ULK3 levels, as measured by immunoblotting in U266 cells. In vivo preclinical model of U266Luc tail vein injection (1x10^6) proved our drugs are highly effective in reducing tumor dissemination and extending overall survival (CTRL untreated n=65 days vs MA9060 n=110). Importantly, we noted no overt toxicity and protected effect against myeloma-induced bone disease. This novel class of drug works synergistically with PI (Bortezomib/Carfilzomib) and can re-sensitize PI resistant disease to these effective therapies. We also show by EMMA ex vivo platform that MA9060 is highly effective for the treatment of CD138+ MM cells isolated from patients with refractory disease. **Conclusions:** ULK3 represents a novel target for treatment of MM refractory disease. Our dual inhibitors can increase overall survival in vivo and ex vivo, therefore we expect to quickly translate our novel molecules to the clinic.

P-116

S-adenosylmethionine biosynthesis is a targetable metabolic vulnerability in multiple myeloma

Yanmeng Wang[1], Anke Maes[1], Kim De Veirman[1], Karin Vanderkerken[1], Eline Menu[1], Elke De Bruyne[1]

[1]VUB

Introduction: Multiple Myeloma (MM) is the second most prevalent hematological malignancy and is incurable due to the inevitable development of drug resistance. Epigenetic modifications induced by metabolic changes play a major role in MM drug resistance. The methionine adenosyltransferase 2α (MAT2A) is a metabolic enzyme that affects DNA and histone methylation, as it is the primary producer of the methyl donor S-adenosylmethionine (SAM). Several studies reported MAT2A deregulation in different solid cancers, showing that silencing of MAT2A resulted in cancer cell death and reduced proliferation. However, its' role in MM is still not clear. Therefore, our study was to clarify the potential role of MAT2A in MM, exploring new therapeutic avenues to overcome drug resistance. **Methods:** The expression of MAT2A in MM patients was analyzed using Genomicscape. The human MM cell lines ANBL6, JJN3 and OPM2 were used to perform in vitro experiments. MAT2A was inhibited by siMAT2A or the specific small molecular inhibitor FIDAS-5. The effects of MAT2A inhibition on cell viability, apoptosis, cell cycle progression and proliferation were determined by CellTiter Glo® Luminescent Cell Viability Assay, Annexin V/7AAD staining, propidium iodide staining and BrdU incorporation, respectively. Downstream pathways and protein synthesis were evaluated using Western Blot and SUnSET method. MAT2A function was also investigated in vivo by using the 5TGM1 murine model. **Results:** MAT2A was found to be highly expressed in patient-derived myeloma cells compared to normal BMPC, correlating with an inferior OS. Direct inhibition of MAT2A, using either siMAT2A or FIDAS-5, impaired the cell viability of JJN3, ANBL6 and OPM2. Mechanistically, we found that FIDAS-5 reduced protein levels of p-mTOR, p-p70, and p-4EBP1 in JJN3 and OPM2, whereas, by knocking down MAT2A, we found a decrease in p-p70, p-S6 and p-4EBP1 levels in ANBL6 and OPM2. These changes suggested a decrease in protein synthesis, which we confirmed in the corresponding cell lines. Furthermore, our results showed that upon MAT2A depletion, proliferation of JJN3 and OPM2 cells was reduced due to a significant accumulation in the G0/G1 and G2-phase. Furthermore, FIDAS-5 was found to induce apoptosis in the three cell lines, by inducing cleavage of PARP, caspase 3, and MCL-1. In vivo, FIDAS-5 was able to reduce the tumor burden in the BM from 54.9% to 26.3%, and the M spike levels from 5.3 g/l to 2.3 g/l in the blood. On protein level, consistent with in vitro results, FIDAS-5 significantly reduced the expression of p-mTOR and p-4EBP1. Finally, we found that both FIDAS-5 and siMAT2A could significantly increase the anti-myeloma effect of the bortezomib in all three cell lines. **Conclusions:** In summary, MAT2A inhibition reduced MM cell proliferation and survival by inhibiting m-TOR mediated protein synthesis. Our findings suggest that the MAT2A inhibitor FIDAS-5 could be a novel compound in bortezomib-based combination therapies for MM.

P-117

High throughput metabolism related drug screening identifies hypoxia inducible factor-1 alpha as a promising therapeutic target in proteasome inhibitor resistant multiple myeloma

Philip Weir[1], Lenka Besse[2], Andrej Besse[2], Christoph Driessen[2], David Donaldson[3], Mary Frances McMullin[4], Lisa Crawford[1]

[1]Patrick G Johnston Centre for Cancer Research, Queen's University Belfast, Northern Ireland; [2]Department of Oncology and Hematology, Kantonsspital St. Gallen, Switzerland; [3]Department of Haematology, Belfast Health and Social Care Trust, Northern Ireland; [4]Centre for Medical Education, Queen's University Belfast, Northern Ireland

Introduction: Multiple myeloma (MM) remains incurable despite many treatments now being available. Proteasome inhibitors (PIs) are highly effective therapies in MM and form a backbone of