pronounced inhibition of cell proliferation ($p = 0.0046$). PI3K inhibition suppressed cancer cell growth, migration and colony formation in vitro. Pan-PI3K inhibition, anti-programmed death 1 (PD1) therapy and combination improved the overall survival (OS) of syngeneic mice with PTEN-deleted tumors from 27 days of the control to 48, 37 and 65 days, respectively. In mice with tumors not containing a PI3K pathway alteration, OS was prolonged by the combination, but not single treatments. Pan-PI3K inhibition significantly upregulated CD80, CD86, MHC-I and MHC-II in dendritic cells, and downregulated the transforming growth factor beta pathway ($p = 0.005$).

Secondary resistance was associated with upregulation of the mammalian target of rapamycin (mTOR) pathway and multiple Spry family genes.

**Conclusions** The combination Pan-PI3K inhibition and ICB has significant anti-tumor effects in aUC with or without activated PI3K pathway and warrant further clinical investigation. This combination creates an immunostimulatory tumor milieu. Secondary resistance is associated with upregulation of the mTOR pathway and Spry family genes. Base on this study, a Phase II clinical trial has been designed.

**Disclosure Information**

C. Pan: None. Z. Zhub: None. S. Zhu: None. A. Ma: None. V.C.S.R. Chittepu: None. H. Farrukh: None. F. Cheng: None.

### Plenary symposium 8: ‘lost in translation’

08.03 **MHGCBASED LARGE-SCALE SCREENING OF ANTI-TUMOR T CELLS IN CHRONIC LYMPHOCTYIC LEUKEMIA REVEALS CD8+ T CELLS WITH SPECIFICITY AGAINST THE CLONOTYPIC B-CELL RECEPTOR IMMUNOGLOBULIN**

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**Background** Chronic lymphocytic leukemia (CLL) remains incurable, indicating a need for novel strategies towards disease eradication, including reinvigoration of anti-tumor immune responses. T cells in CLL appear selected by restricted antigens, with recent evidence suggesting that the selecting epitopes may lie within the clonotypic B-cell receptor immunoglobulins (BcR IGs). Here, we present a large-scale evaluation of T cell recognition towards BcR IGs. We predicted MHC-I binding peptides from such clonotypic regions and determined the presence of T cell recognition towards such sequences, using DNA-barcoded multimers of peptide-major histocompatibility complexes (MHC).

**Materials and Methods** We evaluated 653 peptides derived from the clonotypic BcR IGs of 25 CLL patients across 13 MHC-I alleles based on the MHC-I typing of the patient. We constructed patient-specific peptide-MHC dextran multimers labeled with a unique DNA barcode and a fluorochrome. MHC-multimer binding T cells from PBMC samples where sorted and evaluated through amplification and sequencing of the MHC-attached DNA barcode, to determine the presence of neoepitope reactive T cells.

**Results and Conclusion** Across the 25 patients we observe T cell reactivity towards 3 peptide-MHC specificities, among the 653 evaluated. The T cell responses observed are listed below:

<table>
<thead>
<tr>
<th>Peptide sequence</th>
<th>MHC-I allele association</th>
<th>Peptide-associated region in clonotypic BcR IG</th>
<th>Somatic hypermutation (SHM) position</th>
</tr>
</thead>
<tbody>
<tr>
<td>VTVDATAVYY</td>
<td>A03*01</td>
<td>IGHV4-34 FR3</td>
<td>A to V at position 96</td>
</tr>
<tr>
<td>INLNSLXIRR</td>
<td>A03*01</td>
<td>IGHV4-39 FR2-3</td>
<td>T to I at position 65, Y to L at position 67, S to R at position 74</td>
</tr>
<tr>
<td>YSFTSYWINW</td>
<td>A24*02</td>
<td>IGHV5-10-1 CDR1-2-3</td>
<td>S to N at position 40</td>
</tr>
</tbody>
</table>

These response where further validated using conventionally fluorescence labelled pMHC tetrants. This demonstrates that cancer-specific somatic mutation in the BcR IG can be targets of T cell recognition of CLL, and hence serve as targets for novel immunotherapeutic strategies. The level of such T cell recognition was sparse in the cohort evaluated, but could potential be boosted with immunotherapy.

The data to be presented, was in-part presented at the European Hematology Association (EHA) annual meeting.

**Disclosure Information**


### Plenary session 9: young researcher session

09.09 **ARMORING ANTI-HER2 CAR-T CELLS WITH C-C-MOTIVE RECEPTOR 8 (CCR8) AND A DOMINANT NEGATIVE TGFB RECEPTOR (DNR) TO ENABLE EFFICACY IN SOLID TUMOR MODELS**

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10.1136/jitc-2022-ITOC9.6

**Background** Chimeric antigen receptor (CAR) T cells have shown great efficacy in treating hematological malignancies. Nonetheless, in solid tumors CAR T cells have yet to demonstrate significant clinical efficacy. In solid tumors, CAR T cells are frequently prevented access to tumor tissue and face profound suppression at the tumor site. To overcome this issue,