TH17 AND TYPE 2 CD8+ CYTOKINE SIGNATURES PREDICT IRAEs IN SOLID TUMORS

1Chester J Kao*, 2Soren Charnmasz, 3Madalena Brancati, 4Stephanie L Alden, 5Howard L Li, 1Aanika Balaji, 4Kabeer Munjal, 5Hua-Ling Tsai, 3Ludmila Danilova, 3Alexei Hernandez, 3Nicole Gross, 4Erin M Coyne, 6Sarah M Shin, 5Jennifer Durham, 5Brian Christmas, 5Christopher Thoburn, 3Maximilian F Konig, 2Evan J Lipson, 1Jarushka Naidoo, 2Laura Cappelli, 7Yasser Ged, 5Marina Barrett, 5Julie Brahamer, 7Jean Hoffman-Censits, 9Tanguy Y Seivert, 2Rachel Garonce-Hediger, 6Sanjay Bansal, 1Laura Tang, 7Elizabeth M Jaffee, 6Genentech/Roche Ltd, Basel, Switzerland; 4Genentech, Pearland, TX, USA; 3The Bloomberg-Kimmel Institute for Cancer Immunotherapy, Johns Hopkins University, Baltimore, MD, USA; 2F. Hoffmann-La Roche Ltd, Basel, Switzerland; 5Institute for Cancer Immunotherapy, Johns Hopkins University, Baltimore, MD, USA; 66G Scott Chandler, 8Rajat Mohindra, 9Won Jin Ho, 9Mark Yarchoan. 9Johns Hopkins University School of Medicine, Baltimore, MD, USA; 7The Bloomberg-Kimmel Institute for Cancer Immunotherapy, Johns Hopkins University, Baltimore, MD, USA; 7Genentech, Hoboken, NJ, USA; 8Genentech/Roche, Basel, Switzerland; 2F. Hoffmann-La Roche Ltd, Basel, Switzerland

Background Immune-related adverse events (irAEs) and their associated morbidity/mortality are a key concern for patients receiving immune checkpoint inhibitors (ICIs). A prospective evaluation of the drivers of irAEs in a diverse pan-tumor cohort is needed to identify patients at greatest risk and to develop rational intervention strategies.

Methods We prospectively collected clinical data and blood samples from patients with solid tumors at a single institution who received ICIs as standard of care. Blood samples were collected at baseline and early on treatment (month 1 or 2). We analyzed 32 circulating cytokines with Luminex multiplex assay and utilized Cytoflow by Time-of-Flight (CyTOF) in an enriched cohort to investigate mechanisms of irAEs. Grade 2 or higher irAEs by CTCAE v5.0 were analyzed to enrich for clinically meaningful toxicities. Multi-testing adjustment utilizing false discovery rate (fdr) was performed for the primary irAE Cox model, early fold changes in interleukin (Il)-6, Il-17f, Il-13, and Il-25 were significantly associated with the development of an irAE (table 1, adjusted p<0.05) and stratified patients by optimal cutoffs utilizing max log-rank statistics (figure 1, p<0.05). In the subgroup analysis, Il-6, Il-17f, Il-13, and Il-25 were also significantly upregulated (figure 2, p<0.05) in patients who developed specific irAEs. To identify the cellular populations underlying these cytokine changes, we performed CyTOF on 15 irAE patients matched with 15 non-irAE patients by regimen and tumor type. Higher baseline proportions of two CD8+ T cell populations (CCR3+ and CCR4+), known to secrete type 2 cytokines, were associated with irAEs, while on-treatment persistent elevation of CD8+CCR4+ and peripheral expansion of effector memory Th17+ cells were associated with irAEs (figure 3, p<0.05).

Conclusions In a diverse, pan-tumor cohort, Il-6/Il-17f related Th17 and Il-13/Il-25 related CD8+ type 2 cytokine signatures are associated with the development of irAEs, serving as possible targets for monitoring and therapeutic interventions.

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REFERENCES
1. Kondo T, Takiguchi M. Human memory CCR4+CD8+ T cell subset has the ability to produce multiple cytokines. International Immunology. 2009;21:523–532.

Ethics Approval This study was approved by the Johns Hopkins institution’s Ethics Board #IRB00267960.

Abstract 1245 Figure 1 Kaplan-Meier Curves of cumulative irAE stratified by early treatment cytokine fold changes. (A) IL-6 at cutoff 0.81, (B) IL-17f at cutoff 1.4, (C) IL-13 at cutoff of 1.1, (D) IL-25 at cutoff of 1.6, (E) combined cytokine status. High combined cytokine status was defined as ≥2 cytokines were high, an intermediate status was defined when at least one cytokine was high, and a low status was when all four cytokines were low (median 2 months).

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Abstract 1245 Figure 2  
Log2 transformed early treatment fold change between patients with no irAEs and specific types of irAEs: (A) II-6, (B) II-17f, (C) II-25

Abstract 1245 Figure 3  
Proportion of cell populations. (A) Baseline, (B) On Treatment. Abbreviations: Tc_I = CD8+CCR3+, Tc_II = CD8+CCR4+, Thi7_EM = CD4+CD45RO+RORYT+Ki67+
Abstract Table 1  Significant cytokines in the adjusted time to irAE Cox model. HRs are reported per unit increase in fold change and were adjusted for treatment regimen used (combination anti-PD1/CTLA-4 treatment vs. anti-PD-1/PD-L1 groups). Abbreviations: HR = hazard ratio

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Adjusted HR (95% CI)</th>
<th>P-value</th>
<th>Adjusted P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-13</td>
<td>1.25 [1.11, 1.41]</td>
<td>0.0003</td>
<td>0.006</td>
</tr>
<tr>
<td>IL-25</td>
<td>1.46 [1.18, 1.79]</td>
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<td>IL-6</td>
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<td>0.013</td>
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<td>IL-17f</td>
<td>1.59 [1.19, 2.12]</td>
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<td>0.013</td>
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