Background

The advent of immune checkpoint blockade (ICB) has dramatically improved clinical outcome and long-term survival for patients with metastatic melanoma (MM). However, there remains an area of high unmet need – namely an absence of peripheral and/or on-treatment biomarkers for response.

Work performed by our group characterised the underlying mechanism by which carriers of the minor allele at rs519596115 (~8% European populations) within IL7, encoding the cytokine IL-7 on chromosome 8, have an increased risk of developing toxicity to ICB in patients with MM. Notably, these carriers of this SNP had stable lymphocyte counts pre- and post-ICB, whilst those with the wild type genotype had a net fall in lymphocytes (Intro Figure 1)[2].

In this current work, we seek to:
1. Validate LSI in a replication cohort of patients with metastatic melanoma
2. Explore the role of LSI in other cancers
3. Consider how LSI could be deployed in routine clinical practice

Methods

We also described that carriers of this SNP had an improved survival in MM in the pre-immunotherapy era[1]. Putting these two elements together we considered whether lymphocyte stability could independently predict outcome following ICB.

We therefore developed the Lymphocyte Stability Index (LSI) – simply the post-treatment laboratory lymphocyte count divided by the pre-treatment count. We found that this metric strongly correlated with both progression-free and overall survival in a discovery cohort of patients with MM (Intro Figure 2)[2].

LSI predicts outcome – multiple tumours

In Figure 1 we show Kaplan-Meier survival curves for those with stable LSI (green line) compared to those with unstable LSI (orange line) for patients with MM stratified by those who received the standard treatment (sICB) and those who received a combination treatment (cICB). The HR is 0.38 (95% CI 0.26-0.56, p<0.001).

Conclusions:

Here we describe the Lymphocyte Stability Index (LSI), a novel, dynamic, peripheral blood biomarker which associates with response to ICB across multiple cancers. In patients with MM, a stable LSI is associated with significantly improved progression-free survival (PFS) and overall survival (OS). This finding validated in a separate cohort of patients with MM and replicated across patients with NSCLC. Importantly, those who received sICB with a stable LSI had an OS equivalent to those receiving cICB with stable LSI and significantly superior to those with unstable LSI, regardless of treatment.

The LSI is an extremely simple biomarker for survival following ICB treatment across multiple cancers with an underlying molecular and genetic association. Application of LSI in MM permits effective patient stratification, delineating those in whom single-Agent ICB provides equivalent benefit to combination anti-PD1 and anti-CTLA-4 treatment, potentially sparing them of the associated toxicity burden. If validated in a prospective trial, this marker has the potential to change standard of care approaches to treatment in MM and other cancers.