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### A SET OF EASY AND STRINGENT CRITERIA TO IDENTIFY IMMUNE-RELATED ADVERSE EVENTS (IRAE SCORING SYSTEM, ISS) IMPROVES CORRELATION WITH OUTCOME IN A PHASE 1–2 TRIAL POPULATION

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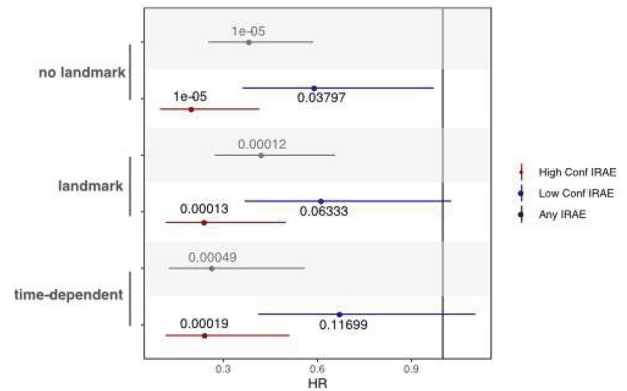
**Background** The benefit from immune checkpoint inhibitors (IO) is tempered by immune-related adverse events (IrAEs), which involve diverse organs, have varying biology, onset time, and severity. Several reports have found correlation between IrAE and better outcome, suggesting they may even serve as a surrogate of response, but studies are conflicting on the magnitude and significance of this correlation. Estimating the true incidence of IrAEs is particularly important in the early phase 1/2 trial setting, in order to avoid the risk of both over- and under-estimation. A key issue is the lack of IrAE diagnostic criteria, necessary to discriminate pure IrAEs from other treatment-related adverse events not sustained by an autoimmune process.

**Methods** Of 421 patients enrolled in phase 1-2 trials, we identified patients treated with immune-oncology (IO) drugs and analysed clinical characteristics, temporal dynamics and correlation with survival of treatment-related events, identifying “High Confidence IrAEs” (HC IrAE) by careful reconsideration of available clinical parameters. We developed an IrAE Scoring System (ISS) based on 5 parameters, each ranging 0-2: available biopsy or specific test, response to immunosuppression, temporal correlation, evidence ruling out alternative cause, known IO relationship. Correlation with Overall Survival was explored by multivariate Cox proportional hazard analysis including multiple covariates (BMI, Age, tumor type, NLR, prior IO, prior Autoimmune disease, PS, baseline disease burden). To mitigate immortal time-bias, analyses were conducted i) at 2-month landmark and ii) modeling IrAEs as time-dependent covariate.

**Results** 204 patients were treated with IO agents (41 with anti-PD(L)1 alone, 33 with non-PD(L)1 agents, 130 with combinations). 53 (25.9%) patients developed  $\geq 1$  treatment-related adverse event (85 total events). ISS score ranged from 0 to 8; by ROC analysis, a cutoff  $\geq 5$  achieved 100% specificity and 90% sensitivity to identify bona fide IrAEs. Based on this, we identified 3 groups of patients: 151 never experiencing an IrAE (“no-IrAE”), 33 low-confidence IrAE with ISS score 0-4 (“LC-IrAE”) and 20 high-confidence IrAE with ISS 5-8 (“HC-IrAE”). Compared to no-IrAE, patients experiencing HC-IrAEs had significantly lower Hazard ratio (HR) both in landmark analysis (HR=0.242, 95% CI 0.117-0.500,  $p=0.0001$ ) and IrAE as time-dependent covariate analysis (HR=0.244, 95% CI 0.116-0.511,  $p=0.0001$ ); HR for patients experiencing LC IrAE, instead, was not statistically significant (figure 1).

**Conclusions** ISS criteria provide a simple system to identify high confidence IrAEs, leading to more reliable estimates of IrAE incidence with significant impact on survival.

**Ethics Approval** The study was approved by the local ethics committee with number UID 3560



**Abstract 1264 Figure 1** Forest plot with Hazard Ratios (points) with 95% CI and p values of patient groups classified by IrAE definition

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