Polygenic risk for skin autoimmunity impacts immune checkpoint blockade in bladder cancer

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PD-1 and PD-L1 act to restrict T cell responses in cancer and contribute to self-tolerance. Consistent with this role, PD-1 checkpoint inhibitors have been associated with immune-related adverse events (irAEs), immune toxicities thought to be autoimmune in origin. Analyses of dermatological irAEs have identified an association with improved overall survival (OS) following anti–PD-(L)1 therapy, but the factors that contribute to this relationship are poorly understood. We collected germline whole-genome sequencing data from IMvigor211, a recent phase 3 randomized controlled trial comparing atezolizumab (anti–PD-L1) monotherapy to chemotherapy in bladder cancer. We found that high vitiligo, high psoriasis, and low atopic dermatitis polygenic risk scores (PRSs) were associated with longer OS under anti–PD-L1 monotherapy as compared to chemotherapy, reflecting the Th17 polarization of these diseases. PRSs were not correlated with tumor mutation burden, PD-L1 immunohistochemistry, nor T-effector gene signatures. Shared genetic factors impact risk for dermatological autoimmunity and anti–PD-L1 monotherapy in bladder cancer.

cancer immunology | autoimmunity | immune-related adverse events | atezolizumab

PD-1 checkpoint inhibitors have made significant advances in metastatic urothelial carcinoma (mUC). Measures of preexisting immunity have been associated with response and survival during anti–PD-(L)1 treatment (1). These measures capture tumor foreignness (i.e., neoepitopes), the accessibility of the tumor to cytotoxic T cells, and tumor (TC) or immune cell (IC) expression of PD-L1. These measures, however, only capture local tumor immunity. In mice, systemic immunity is required for successful tumor rejection by PD-1 checkpoint blockade, and substantial evidence supports the role for host factors in influencing systemic immunity (2, 3). These host factors may include genetic variants that influence innate and adaptive immune responses, including risk for autoimmunity.

The PD-1 immune checkpoint acts to restrict T cell responses and contributes to the regulation of immune self-tolerance (4, 5). Consistent with this role, patients develop immune-related adverse events (irAEs) that are thought to be autoimmune in origin, but the link is poorly understood (6, 7). Indeed, in mice, on vulnerable genetic backgrounds, spontaneous autoimmunity develops on knockout of PD-1. Yet, whether genetic background is relevant to development of irAEs in humans has not been tested. irAEs also vary in their frequency and organ system affected. Among the most common irAEs are those that occur in the skin. Intriguingly, dermatological irAEs have also been associated with longer overall survival (OS) across PD-1 checkpoint inhibitors (8–12). To gain further insight into this relationship, we used genetic variants known to impact risk of psoriasis (PSO), vitiligo (VIT), and atopic dermatitis (AD) ascertained in independent cohorts by genome-wide association study (GWAS). Using these variants, we computed polygenic risk scores (PRSs) for patients treated with atezolizumab or chemotherapy in IMvigor211 and associated them with dermatological irAE occurrence and OS.

Results

To examine the relationship between safety and efficacy of checkpoint blockade, we conducted an analysis of irAEs using

Significance

PD-1 checkpoint inhibitors target the immune system to induce antitumor immunity. Because germline genetic variation contributes significantly to variation in immune responses, we collected whole-genome sequencing data from patients who provided informed consent in a recent bladder cancer trial, comparing a PD-L1 inhibitor to chemotherapy, to determine whether genetics could contribute to a patient's response to this class of cancer drugs. We found that genetic variants that confer risk for dermatological autoimmunity impact patient survival, as compared to chemotherapy, and risk of skin toxicity during treatment. Our data provide evidence that genetics influences a cancer patient's immune set point. Further study of genetic variants associated with autoimmunity and the genes they perturb may provide the basis of novel immunotherapies.

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Competing interest statement: The authors declare a competing interest. Z.K., F.D.N., A.K., C.H., S.M., V.R., J.C., M.F., S.L.A., E.G., H.C.-H., T.B., I.M., J.H., and G.S.C. are employees of Genentech/Roche. Z.K., G.S.C., and M.L.A. are inventors on a pending patent filed by Genentech/Roche on the use of polygenic risk scores for dermatological autoimmune diseases as methods for patient selection for treatment with immune checkpoint inhibitors. J.R. reported receiving personal fees and other support from Seattle Genetics, Astellas, Merck, Genentech/Roche, Bayer, AstraZeneca, Chugai, QED, and Bristol-Myers Squibb; personal fees from UpToDate, Eli Lilly, Inovio, Bioclin/Ranier, Adicet Bio, Sensei Biotherapeutics, Pharmacyclics, GSK, Janssen, and Western Oncolytics; as well as other support from Illumina. In addition, J.R. has a patent to predicting cisplatin sensitivity pending. T.P. has received research funding/honoraria from AstraZeneca, Genentech/Roche, Bristol-Myers Squibb, Merck, MSD, Pfizer, Exelixis, Astellas, and Johnson & Johnson. M.L.A. was previously an employee of Genentech/Roche and is currently an employee of insitro.

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Data deposition: An R package with anonymized data and code to reproduce the computational methods in the manuscript is available at http://research-pub.gene.com/CITSkinSurvival.

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data from safety-evaluable patients (n = 459) receiving atezolizumab in IMvigor211 (13). We grouped irAEs using an organ and system-based classification (see *Methods*). Skin irAEs were the most common, followed by gastrointestinal and endocrine irAEs (Fig. 1*A*). We confirmed a similar distribution of irAE in IMvigor210 (n = 429), a phase 2 single-arm trial for treatment of mUC (14, 15). We focused on low-grade irAEs as they are typically managed without systemic corticosteroids and rarely lead to discontinuation of treatment (16). To address survival bias, we used a time-dependent covariate in a Cox proportional hazards model, including baseline factors as additional covariates (see *Methods*). In agreement with previous reports linking dermatological irAEs to survival (8–12), we found that OS was associated with low-grade skin irAEs in IMvigor211 (P = 0.024; HR 0.66; 95% CI 0.45–0.95) and IMvigor210 (P = 0.0023; HR 0.53; 95% CI 0.35–0.80; Fig. 1*B*). To verify the robustness of our results, we conducted a landmark analysis. We selected landmarks at the point at which 90% patients in the low-grade skin irAE group had experienced their event (Fig. 1*C*) and confirmed an association with improved OS in both trials (Fig. 1*D*).

Germline whole-genome sequencing (WGS) data from 465 individuals within the IMvigor211 study (238 receiving atezolizumab and 227 chemotherapy treated) met strict filters for population and genotype data quality control (see *Methods*). We confirmed that OS and response rates were no different in these individuals, as compared to the intent-to-treat population of 931 individuals (*SI Appendix*, Fig. S1). We also confirmed that IC and TC staining of PD-L1 by immunohistochemistry (IHC) and tumor mutation burden (TMB) were similarly balanced across trial (*SI Appendix*, Fig. S2).

To test the hypothesis that genetic factors shared with dermatological autoimmunity impact anti–PD-L1 safety and efficacy, we used publicly available GWAS summary statistics to construct PRSs for PSO, AD, and VIT which were ascertained on independent case/control cohorts (see *Methods* and Fig. 2*A* and *SI Appendix*, Table S1 and Fig. S3) (17, 18). We used two

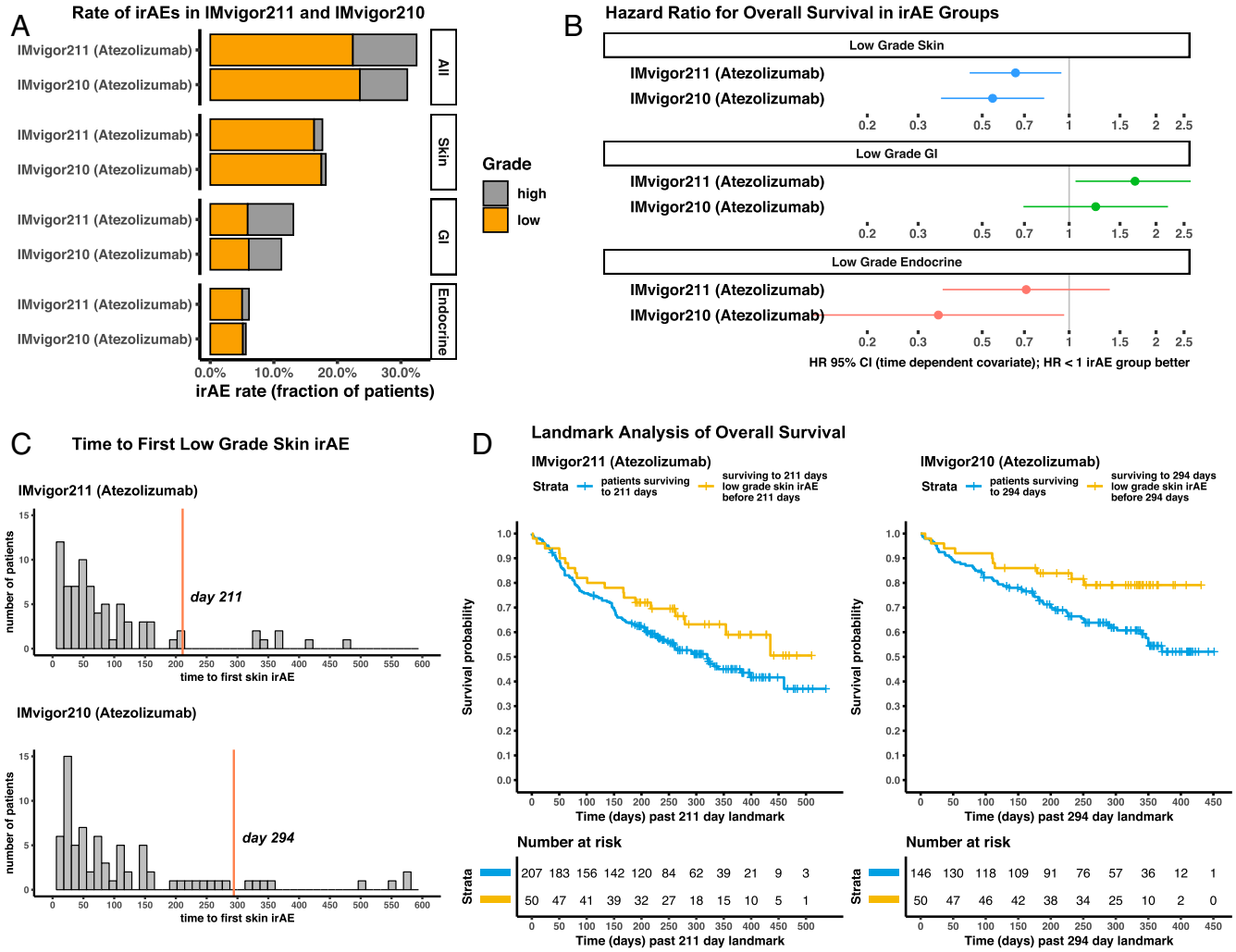

Fig. 1. Low-grade dermatological irAEs in patients receiving atezolizumab are associated with longer OS. (*A*) Rate of irAEs, aggregated by system- and organ-based classification, across trials. Only irAE categories with occurrence rates >5% are shown. Low = grade 1 or 2 (orange stacking bar); High = grade 3, 4, or 5 (gray stacking bar). (*B*) Hazard ratios (HRs) with 95% CIs are shown as thick lines, comparing OS of individuals that experienced low-grade irAEs to those that did not experience irAE of a given classification. Individuals that experienced a high-grade irAE of the given classification were excluded from the analysis. A time-dependent covariate in a Cox proportional hazards model was used to estimate the HRs (see *Methods*). (*C*) Distribution of time to first skin irAE in days across trials. Ninety percent of patients that experienced skin irAEs lie to the left of the orange landmark line. (*D*) Kaplan-Meier survival curves comparing the OS of individuals in the atezolizumab arm of IMvigor211 and IMvigor210 after a defined landmark. Tick marks show censoring events. GI = gastrointestinal.

studies for PSO, Immunochip (PSO/IC) and the UK Biobank (PSO/UKBB). PSO/IC assessed genotypes curated for immunologically relevant variants, whereas PSO cases in PSO/UKBB were self-reported and assayed using genome-wide genotyping. We additionally constructed PRSs for Alzheimer's disease (ALZ) to serve as negative controls. Controlling for genotype principal components (PCs) and sex, we identified associations at a false discovery rate (FDR) of 10% between the occurrence of skin irAEs and genetic risk for PSO within the atezolizumab arm of IMvigor211 (Fig. 2*B* and *SI Appendix*, Table S2). The associations were consistent across GWASs used to construct the PSO PRSs (Fig. 2*C*). Although the Nagelkerke pseudo-R^2 was only 0.12 for the PSO/IC (1e-08) PRS, we confirmed that the association observed was also reflected in the time to adverse event data (*SI Appendix*, Fig. S4).

Given the observations that dermatological irAEs are associated with longer OS, and germline genetic risk for PSO is associated with increased odds of skin irAEs during checkpoint blockade, we investigated whether dermatological autoimmune disease PRSs were associated with OS under atezolizumab treatment or chemotherapy (analyzed independently). PRSs for AD, PSO, and VIT were associated with OS in the atezolizumab arm, but not the chemotherapy arm, of IMvigor211 at an FDR of 10%, controlling for baseline clinical factors in addition to genotype PCs (Fig. 2*D* and *SI Appendix*, Table S2; also, see *Methods*). PRSs for ALZ, as expected, did not show any significant association. The GWAS *P* value cutoffs at which we observed significant associations differed between OS and skin irAEs, as well as across diseases, reflecting the differing degrees of genetic sharing and statistical power of the GWASs underlying the PRSs (see *SI Appendix*, *Supplemental Discussion*). We also highlight that the T-effector gene signature, a measure of $CD8^+$ T cell effector function within a tumor, was the unique

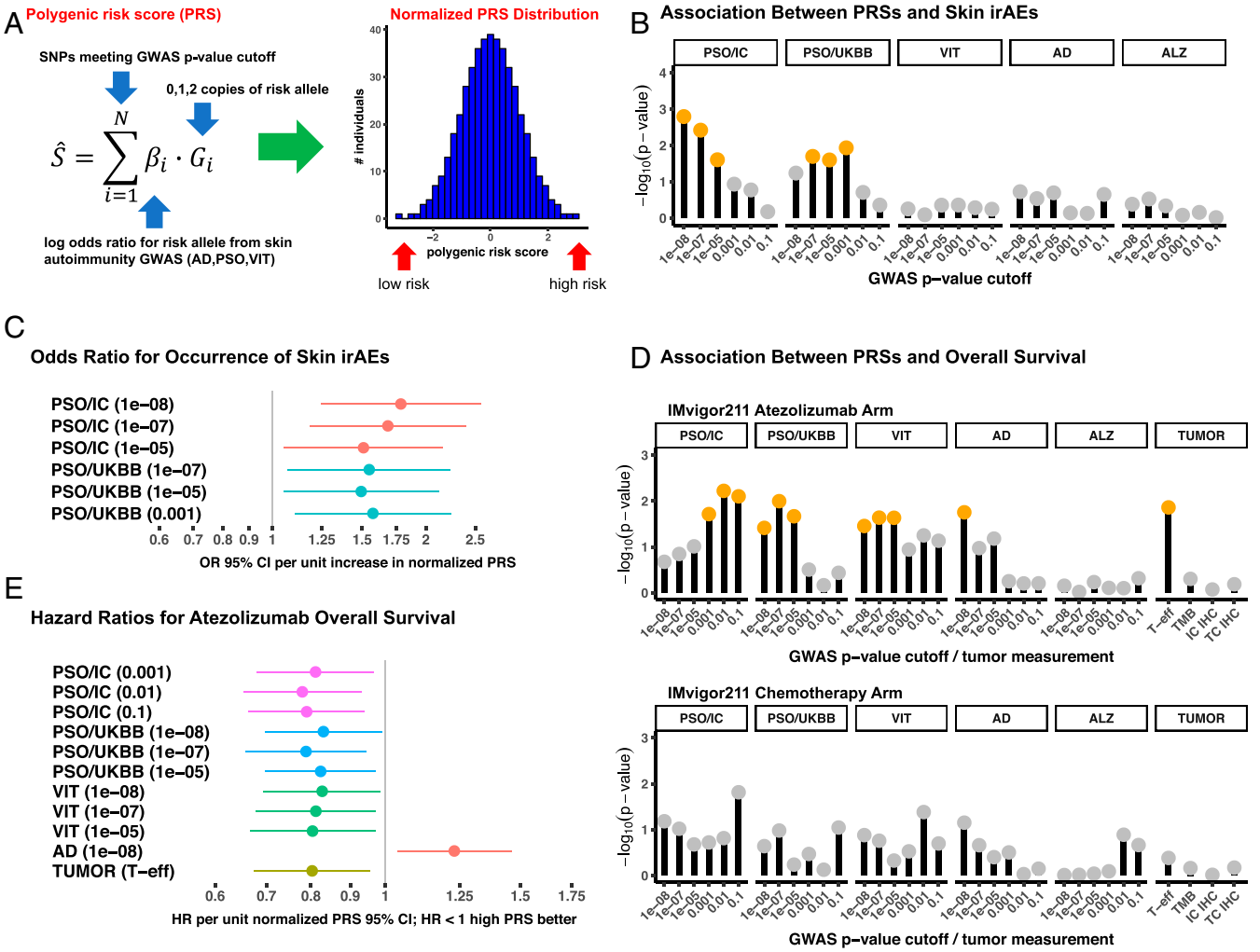

Fig. 2. Polygenic risk for skin autoimmunity is associated with the occurrence of dermatological irAEs and OS in the atezolizumab arm of IMvigor211. (*A*) PRSs were computed for each individual with whole-genome germline sequencing data in IMvigor211 for dermatological autoimmune diseases: AD, PSO, and VIT. PRSs were constructed for 6 *P* value cutoffs (see *SI Appendix*, Table S2 and *Methods*). (*B*) Negative $\log_{10}$ *P* values for a given PRS testing for association with occurrence of skin irAEs controlling for five genotype principal components and sex by logistic regression. Orange circles show associations that were significant at an FDR of 10%. Gray circles did not meet statistical significance. (*C*) Odds ratios and 95% CIs were estimated for PRSs and skin irAE occurrence for PRSs that met a significance cutoff of FDR 10%. ORs are expressed in per-unit change of a normalized PRS. GWAS *P* value cutoff indicated within parentheses. (*D*) Negative $\log_{10}$ *P* values for a given GWAS and *P* value cutoff PRS testing for association with OS using a Cox proportional hazards model controlling for five genotype principal components and baseline clinical factors (see *Methods*). (*E*) Adjusted HRs and 95% CIs for PRS and OS associations are shown, using significance cutoff of 10% FDR. HRs are expressed in unit change of a normalized PRS. IC = Immunochip; T-eff = CD8 T-effector gene expression signature score; IC IHC = PD-L1 expression on immune cells; TC IHC = PD-L1 expression on tumor cells.

tumor factor significantly associated with OS within the atezolizumab arm in the IMvigor211 [confirming prior studies (14)].

Both increased polygenic risk for VIT and PSO were associated with longer OS under treatment with atezolizumab, whereas decreased polygenic risk for AD was associated with longer OS under atezolizumab treatment (Fig. 2*E*). We confirmed that the OS associations were not simply due to correlation between the T-effector signature or strong intercorrelation among the disease-specific PRSs (*SI Appendix*, Fig. S5). We quantile-normalized the T-effector signature score to allow comparison to quantile-normalized PRSs. The HR benefit of a higher T-effector signature score per normalized unit was 0.81, similar to that of the PRSs per normalized unit for PSO, VIT, and the inverse of AD 0.78–0.83.

We then assessed whether PRSs were prognostic, informative of outcome regardless of treatment, or predictive, informative of the effect of experimental treatment. To formally test if PRSs were predictive, we incorporated both trial arms into a Cox proportional hazards model and assessed interaction between the PRS and trial arm. After controlling for baseline clinical covariates and genotype PCs, a significant trial arm by PRS interaction term tests whether the HR comparing atezolizumab to chemotherapy differs between patients with high versus low PRSs (see *Methods*). At an FDR of 10%, we found that PRSs for AD, PSO, and VIT were predictive of OS in IMvigor211 (Fig. 3*A* and *SI Appendix*, Table S2). Consistent with prior reporting of the IMvigor211 study, tumor measurements were not strongly predictive of OS (13). We extended this analysis to consider 10 additional autoimmune diseases across 11 different cohorts. We found that our observations were largely limited to the immune-mediated dermatological diseases we considered (*SI Appendix*, Table S3 and Fig. S6).

To better understand the behavior of the PRSs, we split the population on median PRS, creating two subgroups of individuals with high and low polygenic risk. We focused on the respective PRSs that had the strongest trial arm by risk score interaction for each dermatological autoimmune disease. High VIT ($P = 0.0016$; HR 0.58; 95% CI 0.41–0.81) and high PSO risk ($P = 5.5 \times 10^{-5}$; HR 0.50; 95% CI 0.36–0.70) individuals had better OS under checkpoint blockade than chemotherapy, whereas low AD risk ($P = 0.0008$; HR 0.57; 95% CI 0.41–0.79) individuals had improved OS under atezolizumab treatment as compared to chemotherapy (Fig. 3*B* and *SI Appendix*, Figs. S7–S9). PRSs were uncorrelated tumor IC staining of PD-L1 by IHC, TMB, and across patients (Fig. 3*C*). To gain further insight into the PRSs, we compared high and low PRS subgroups within each treatment arm (Fig. 3*D*). High VIT risk reflected improved OS in the atezolizumab arm, whereas high PSO risk and low AD risk groups reflected both improved OS in the atezolizumab arm and worse OS within the chemotherapy arm. As response is a proxy for longer and shorter OS, we found that the response rates within these subgroups followed a similar numeric pattern (*SI Appendix*, Fig. S10).

Variants in the major histocompatibility complex (MHC) locus and specific human leukocyte antigen (HLA) alleles contribute significantly to genetic risk for PSO, VIT, and AD (*SI*

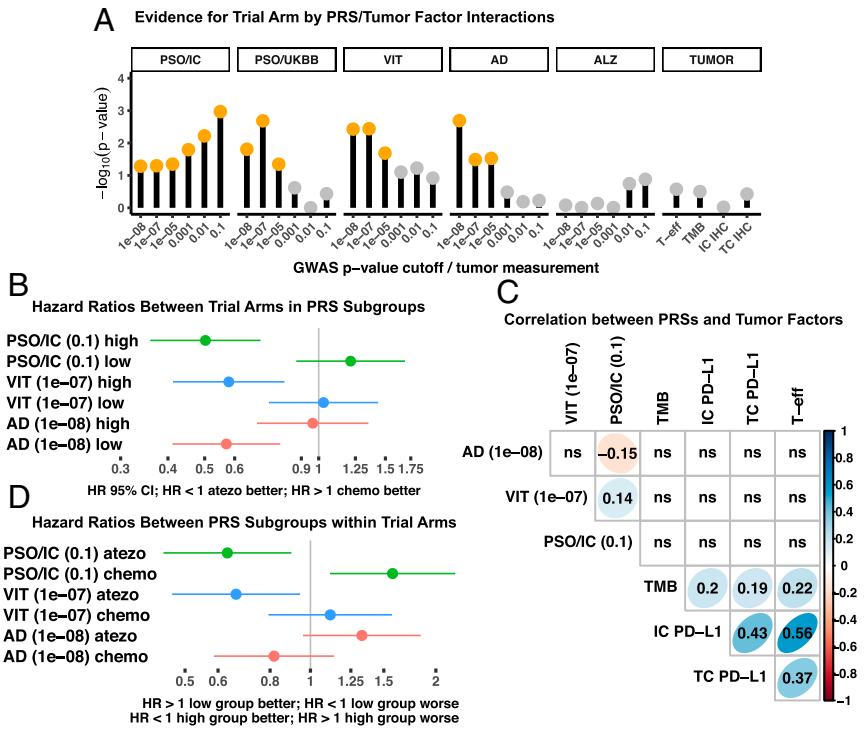

Fig. 3. PRSs for dermatological autoimmunity are informative of the effect of treatment in IMvigor211. (*A*) Negative $\log_{10}$ *P* values for a given PRS testing for a statistically significant trial arm by PRS/tumor factor interaction using a Cox proportional hazards model for OS, controlling also for five genotype PCs, sex, and clinical covariates (see *Methods*). Orange circles designate PRS and trial arm interaction terms that were significant at an FDR of 10%. Gray circles indicate values that did not meet statistical significance. (*B*) HRs and 95% CI for Cox proportional hazard models are shown, comparing trial arms in subgroups of high and low risk for PRSs that showed the strongest trial arm by PRSs interaction. HRs were adjusted for baseline clinical covariates, genotype PCs, and sex (see *Methods*). High- and low-risk groups were defined by splitting the population on the median. Respective GWAS *P* value cutoff of the corresponding PRS is indicated in parentheses. (*C*) Spearman's rank correlation between PRSs and tumor factors across individuals in IMvigor211. Rank correlations with $P \geq 0.05$ are labeled ns. T-eff = CD8 T-effector gene expression signature score; IC PD-L1 = immune cell PD-L1 expression by IHC; TC PD-L1 = tumor cell PD-L1 expression by IHC. (*D*) HRs and 95% CIs from Cox proportional hazard models are shown comparing OS of subgroups of high and low risk for PRSs within each trial arm. atezo = atezolizumab; chemo = chemotherapy.

Appendix, Table S4) (19–21). As our PRSs were generated using a reference panel that poorly approximated linkage disequilibrium (LD) in the MHC region, we excluded variants from this region in our association analyses. To address this caveat, we repeated our analysis including variants in the MHC region. Inclusion of this additional information did not strengthen the associations we observed (*SI Appendix*, Fig. S11). We also called HLA alleles on the basis of direct sequence evidence (see *Methods*). We found that HLA alleles previously found to be associated with risk of PSO, AD, or VIT were not associated with OS in the atezolizumab or the chemotherapy arm of IMvigor211 (*SI Appendix*, Table S5). As these alleles may contribute additively to risk of dermatological autoimmunity, we incorporated the risk conferred by these alleles to our PRSs (see *Methods*). Inclusion of this additional information had negligible impact (*SI Appendix*, Fig. S11).

The tumor microenvironment (TME) consists of a complex mixture of immune cells, stromal, and tumor cells (22). Polygenic

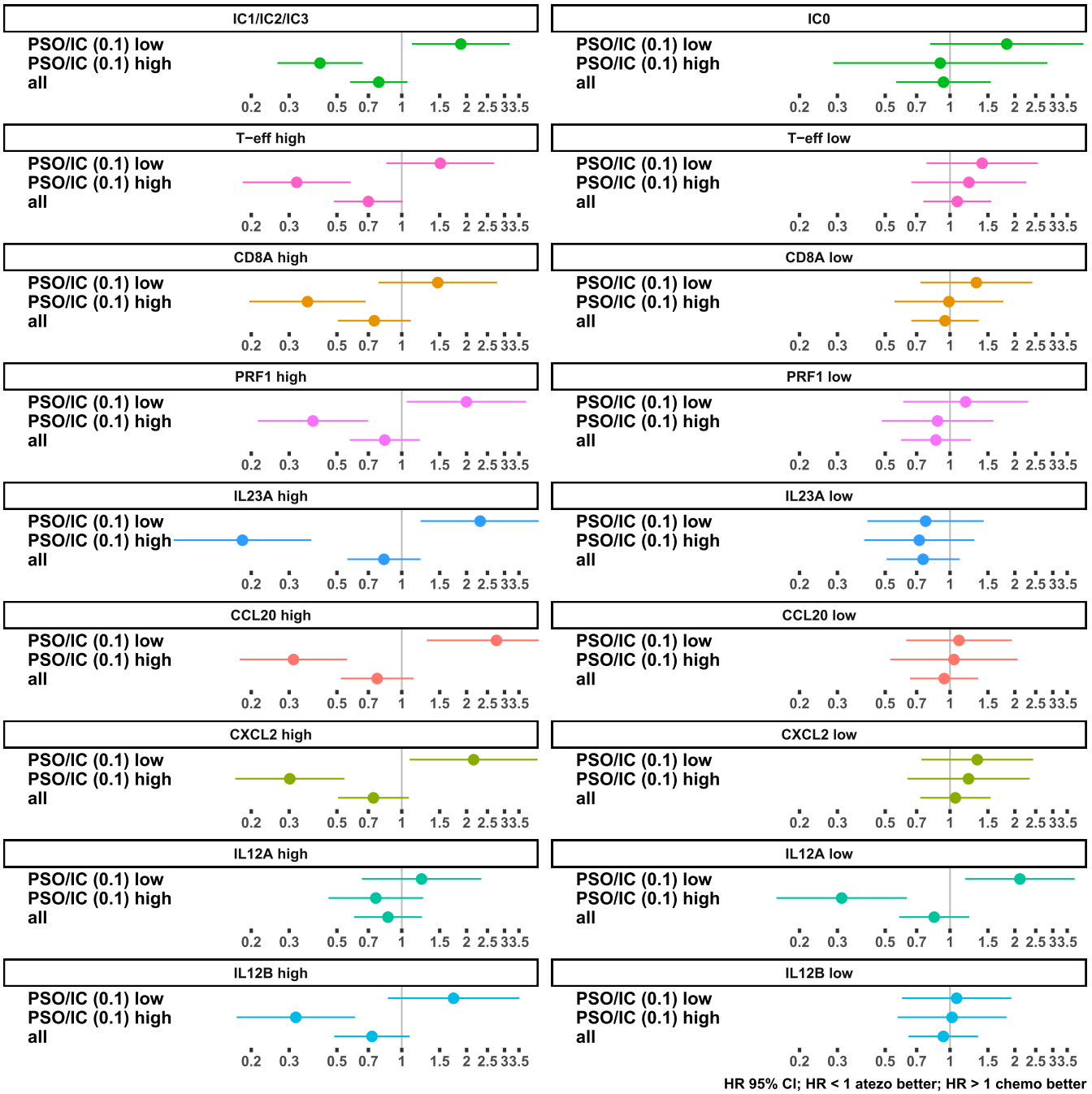

Fig. 4. Polygenic risk for PSO is informative of the effect of treatment in specific tumor immune contexts. HR and 95% CI compare the trial arms. Patients are stratified by of high or low tumor factor across the two columns. Within each row, patients are stratified by high or low risk for PSO using the PSO/IC PRS at a GWAS *P* value cutoff of 0.1. "All" designates no PRS stratification. HRs were adjusted for RNA-seq batch effects, baseline clinical covariates, genotype PCs, and sex (see *Methods*). High or low PRS groups and high or low tumor gene expression groups were defined by splitting the population on their median values, respectively. IC0-3 designates increasing levels of IC staining of PD-L1 by IHC. Only tumor factors and genes that met defined filtering criteria (*SI Appendix*, Table S5) and were significant at an FDR of 10% are shown here (see *SI Appendix*, Table S6 and Fig. S13 for all tested PRSs, genes, and tumor factors).

risk may influence the composition of the TME, which in turn impacts patient survival. Using pretreatment, bulk tumor gene expression for $n = 398$ individuals with both RNA-seq and germline genetic data, we generated immune and stromal cell-type enrichment scores, and, to limit the multiple testing burden, we associated them with PRSs that had the strongest trial arm by risk score interaction for each dermatological autoimmune disease (23). We found no evidence for association between cell-type enrichment scores and PRSs (*SI Appendix*, Fig. S12). Alternatively, PRSs might be relevant only in certain tumor contexts. To address this question, we delineated four subgroups on the basis of high or low PRS and a high or low tumor factor. Specifically, we considered: PD-L1 expression measured by IHC and expressed on ICs or TCs, TMB, and the CD8 T-effector signature. We additionally considered the tumor expression of selected T-helper chemokines and cytokines involved in differentiation, recruitment, and response (*SI Appendix*, Table S6). We statistically assessed whether combining a PRS and a tumor factor was more informative of the treatment effect on OS than the PRS alone (see *Methods*). This would occur if the treatment effect depended on both the PRS value and the tumor factor value (*SI Appendix*, Fig. S13). We found high-PSO PRS was beneficial in immune-infiltrated tumors as reflected by survival benefit in tumors with high values of IC staining of PD-L1 by IHC and high expression of genes involved in $CD8^+$ T-effector function. Although little or no pretreatment *IL17A/F* expression was detected by bulk RNA-seq, above median expression of genes involved in Th17 function including *IL23A*, *CXCL2* and *CCL20* when combined with the PSO PRS also delineated a subgroup that benefited from atezolizumab as compared to chemotherapy (Fig. 4). This subgroup existed in the absence of any correlation between PSO PRS and these tumor factors or overlap with patients with high T-effector scores (*SI Appendix*, Fig. S14). As both expression measures were uncorrelated, we found that the survival benefit of high-PSO PRS was strongest in patients with tumors that had both high *IL23A* expression and T-effector scores (*SI Appendix*, Fig. S15). We also observed a divergent pattern between PSO PRS and expression of subunits of IL-12 (*IL12A* and *IL12B*) in a manner consistent with preclinical observations of the divergent roles of IL-12 and IL-23 in autoimmunity (*SI Appendix*, *Supplemental Discussion* and Figs. S16 and S17).

Discussion

Dermatological irAEs have been associated with longer OS across PD-1 checkpoint inhibitors (8–12). Using germline WGS data from a phase 3 trial comparing anti–PD-L1 monotherapy to chemotherapy in mUC, we found that PRSs for dermatological autoimmune diseases were associated with increased risk for skin irAEs and longer OS with atezolizumab, as compared to chemotherapy. We note that, while AD is not classically considered an autoimmune disease, recent studies have identified autoimmune mechanisms in the chronic phase, and GWASs have identified susceptibility loci near genes linked to autoimmune disease (24). Our study provides further insight into the relationship between dermatological irAEs and patient survival. Our analysis indicates that genetic factors that modify individual risk of dermatological autoimmunity also impact PD-L1 blockade in this setting. Further study of the mechanisms and genes by which these variants act may provide important insights for the basis of novel cancer immunotherapies and may aid in the management of patients undergoing checkpoint inhibitor therapy. The directionality of the association with OS and PRSs for PSO and VIT versus AD reflected the high and low Th17 polarization of these diseases in European (EUR) populations, respectively (*SI Appendix*, *Supplemental Discussion*) (25, 26). However, further molecular and cellular profiling of irAEs, systemic immune responses, and tumors, before and during treatment, is needed to establish whether Th17 cells are primary or secondary mediators. Taken together, our observations support the notion that an immune set point, at least in part determined by germline genetic variation, may influence the efficacy of immune checkpoint blockade (1).

Although useful to provide insight into the role of germline genetics during PD-L1 blockade, several important challenges remain before PRSs can contribute to clinical decision making. PRSs derived from GWASs conducted in EUR populations will have reduced accuracy in populations of Asian and African descent (27). PRSs are also limited by disease heritability and sample size of the underlying GWAS. PRS associations with phenotypes not analyzed in the original case–control GWAS establish the presence of shared genetic factors, but the precise extent of shared loci is difficult to establish from a PRS alone. Further studies are needed to establish the contexts where PRSs might be relevant and to delineate their interactions with tumor factors in patients treated with immune checkpoint inhibitors.

Methods

Patient Cohorts. We conducted our analysis of irAEs in the safety-evaluable population from IMvigor211 (NCT02302807) and IMvigor210 (NCT02951767, NCT02108652). irAEs were captured using an Adverse Events of Special Interest strategy across these trials. Protocols, sites, participating investigators, and confirmation of an independent ethics committee approval of each protocol at each site is provided in the original IMvigor211 and IMvigor210 publications (13–15). Confirmation of informed consent for research on germline DNA for this study was provided by the Ethics Lead in Biosample & Repository Management at F. Hoffmann-La Roche AG.

Germline WGS. We sequenced genomic DNA isolated from blood samples from $n = 479$ individuals from IMvigor211 on the basis of availability and informed consent for research on germline DNA. DNA was extracted using the DNA Blood400 kit (Chemagic). DNA was sheered (Covaris LE220), and sequencing libraries were prepared using the TruSeq Nano DNA HT kit (Illumina, Inc.). Libraries were sequenced at Human Longevity. The 150-bp paired-end WGS data were generated to an average read depth of 30× using the HiSeq platform (Illumina X10). Joint genotyping was performed using Genome Analysis Toolkit followed by filters for variant and population data quality control. We used HLA*PRG:LA (retrieved March 8, 2017, git commit SHA-1 hash prefixed by 7b9ba45) to infer HLA alleles at G group resolution. Details are provided in *SI Appendix*.

Construction of PRSs. All PRSs were constructed by pruning and thresholding using publicly available GWAS summary statistics. We used an LD reference panel, the EUR population from the 1000 Genomes Project, to approximate LD that would be present in the original case control populations for each of the GWAS of these diseases. Associations between irAE occurrence, OS, and PRSs were performed in R. Details are provided in *SI Appendix*.

Code Availability. An R package with anonymized clinical data; precomputed normalized PRSs; precomputed HLA calls for VIT, PSO, and AD risk alleles; and all R code to produce figures in the manuscript has been made available for download: http://research-pub.gene.com/CITSkinSurvival.

Data Availability. Anonymized patient-level clinical data and summary-level PRS data are available within the R package described above. All requests for genotype (VCF) or raw data (BAM/FASTQ) will be promptly reviewed by Roche/Genentech to verify if the request is subject to patient consent and confidentiality obligations. Any data that can be shared will be released through establishment of a data-sharing agreement with Roche/Genentech. Please contact the corresponding authors for any inquiries regarding the requests for data.

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