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Original Article

Patient Blood Type Is Associated With Response to Immune Checkpoint Blockade in Metastatic Cancer

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Abstract

Background: Immune checkpoint blockade (ICB) has transformed cancer therapy, with long-term responses and a favorable safety profile; however, only a minority of patients respond. Response to ICB is influenced by immune-related genetic factors such as HLA haplotype, potentially including patient blood type and associated differences in diversity of the T-cell repertoire. A minority of patients experience immune-related adverse events (irAEs), with unclear relation to response or resistance.

Materials and Methods: In this single institution study, we aimed to investigate the relationship of time to treatment failure (TTF) with patient blood type and with occurrence of irAEs, among patients with metastatic cancer receiving ICB.

Results: We found a strong association of improved TTF with presence of irAEs, and also among patients with type O blood, compared with type A/B/AB blood. Among patients with type O blood, TTF was substantially longer among those experiencing an irAE (n = 44; adjusted HR 0.41, 95% CI 0.18,0.96). For patients with type A/B/AB blood, no significant association was present (n = 63; adjusted HR 0.69, 95% CI 0.39,1.21). For type O patients, median TTF of ICB was 13.4 months (95% CI: 3.79 months, NA) vs 2.55 months (95% CI: 1.95 months, 4.95 months) for other patients.

Conclusion: This retrospective study of a cohort of patients receiving ICB suggests a preferential benefit among patients with type O blood and, in particular, among patients with type O blood who developed irAEs. Validation in future independent cohorts and investigation of a potential biologic basis for this finding is warranted.

Key words: blood type; immune checkpoint blockade; immune-related adverse events; time to treatment failure.

Implications for Practice

The findings of this study require validation in larger cohorts but suggest that there may be an opportunity for therapeutic modulation with vaccination approaches and for identification of promising patient populations for immune checkpoint blockade. If confirmed, these findings might support investigation of future therapeutic strategies to overcome blind spots in the T-cell immune repertoire.

Introduction

Immune checkpoint blockade (ICB), with inhibitors that target CTLA-4, PD-1, or PDL1, has greatly improved treatment of metastatic cancer, with the potential for long-lasting remission in some patients. However, only a minority of patients with metastatic cancer respond. Biomarkers which predict response to ICB include tumor genomic aberrations, increased PD(L)1 expression levels and other expression signatures in the tumor microenvironment, and also host germline genetics[1] including HLA genotype.[2,3] Although ICB is associated with fewer toxic adverse events than standard chemotherapy, some patients experience severe immune-related adverse events (irAEs), which can affect the colon (colitis), lung (pneumonitis), or other organs, and their management often requires immunosuppression in the form of corticosteroids. Finally, some studies find that the presence of irAEs is predictive of response to ICB and improved overall survival,[4-7] while other studies[8,9] do not find such an association.

A major driver of response to ICB is hypothesized to be the diversity and quality of the immunogenic neoantigen repertory.[10,11] Immunogenic neoantigens are tumor-specific mutated peptides which can be presented to and recognized by the patient's T-cell receptor repertory. Increased immune diversity, in the form of maximal heterozygosity in the patient's HLA genotype in particular, has been demonstrated to be associated with a greater diversity of antigens which can be presented to the immune system, and thus a greater diversity of immunogenic neoantigens, and hence with improved response to ICB.[2,12,13]

A second genetic factor that may potentially contribute to immunogenic neoantigen diversity may be blood type,[14,15] which is a blood classification system based on the presence

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or absence of a set of inherited antigenic cell surface markers (proteins, carbohydrates, or glycolipids) on red blood cells. For example, in the A/B/O blood-type system each person is either classified as either type A (presence of type A antigens on red blood cells), type B (presence of type B antigens on red blood cells), type AB (presence of both antigen types), or type O (absence of both antigen types on red blood cells). In persons with type O blood, there are circulating antibodies to type A and type B antigens, indicating that the immune system recognizes the associated type A and B peptides. However, in type A/B/AB blood, the associated peptides have been recognized and processed as "self", and any immune response to these peptides has consequently been negated.[3] Thus, in type O blood when compared with type A/B/AB blood, there is reduced negative selection of autoreactive T cells and consequent increased relative diversity of the T-cell receptor repertory.

To investigate this hypothesis, in this report we study a series of patients with metastatic solid tumors (including metastatic lung, skin, head and neck cancer, and other cancer types) treated with ICB at UCSD between 1/1/2014 and 1/1/2019. We investigate the association between irAEs, blood type, and time to treatment failure (TTF; ie, discontinuation of therapy) in these patients. Time-to-treatment failure includes discontinuation due to adverse events, disease progression, or death, and was used as our primary outcome as it is a clinically relevant measure which includes potential discontinuation due to irAEs, and also to avoid confounding from subsequent sequential therapeutic regimens in these patients with metastatic disease.

Materials and Methods

Study Participants

This retrospective chart review was approved by the UCSD Institutional Review Board. Medical records including radiology reports from consented immunotherapy recipients seen at UCSD from 1/1/2014 to 1/1/2019 were extracted using EMR search functionality and manually reviewed. All data were de-identified, following HIPAA regulations. Inclusion criteria were a diagnosis of metastatic cancer (including lung, skin, head and neck, and other cancer), receiving anti-PD-1 or anti-CTLA-4 directed therapy, and the presence of blood type information in the EMR, which is usually obtained prior to surgery. Patients were routinely seen in the clinic to assess any irAE to immunotherapeutic drugs and to evaluate treatment response. Subjects were excluded if imaging and toxicity records were not available. For each patient, the date of onset and termination of each sequential treatment regimen was abstracted. Type of treatment within each regimen was categorized as anti-CTLA-4 therapy, anti-PD-(L)1 therapy (including anti-PD1 and/ or anti-PD-L1therapy), or combination therapy (including targeted therapy and/ or chemotherapy) with anti-PD-(L)1 therapy.

Outcome and Exposures of Interest

Time to treatment failure was defined as time from ICB therapy initiation to discontinuation of ICB for any reason including disease progression, toxicity, or death. As patients may have more than one sequential treatment with ICB, we used the earliest or first treatment regimen in patient's medical record in the primary analysis. Progression was ascertained by assessment of imaging in the electronic medical record, and timing was noted to the nearest month; patients who were still on ICB therapy and had not progressed were noted as censored. Patients' blood type was combined into the 4 sub-groups blood type A, B, AB, and O. Our main comparison of interest is type O blood vs type A/B/AB blood, due to the potential for broader immune surveillance of potential neoantigens of type O blood compared with type A/B/AB blood. Adverse events were manually coded as irAEs based on clinician note indicating any irAE or use of immunosuppression (ie, prednisone, infliximab, etc.), as per the NCCN Management of Immunotherapy-Related Toxicities Guideline.[16] We coded an indicator for occurrence of irAE as 1 if any irAE occurred at least once during a treatment regimen and 0 otherwise.

Covariates

Potential confounders were basic demographics (age, gender, race/ethnicity), type of ICB treatment and histologic site. Cancer types were combined into 4 categories: melanoma, lung, head and neck, and other (breast, endocrine, genitourinary, GI, GYN, heme, neurological tumors, and soft-tissue sarcoma). Treatment type was coded as binary (Yes/No) for each of anti-CTLA-4 therapy, any anti-PD-(L)1 therapy and anti-PD(L)1-containing combination therapy (including immunotherapy, targeted therapy, or chemotherapy).

Statistical Methods

All tests were two-sided at 5% significance level, carried out in R (3.6.0). Kaplan-Meier plots and the log-rank test were used to investigate univariate associations of the exposures of interest irAE (presence vs absence) and blood type (type O blood vs type A/B/AB blood) with the outcome TTF among the first recorded treatment regimen of each patient. We used multivariable Cox-proportional hazard regression to adjust for potential confounders. For multivariable models, we started with all confounders included in the model and used backward selection with the exclusion P-value set to .3; age and treatment types were retained during selection. After selection of confounders, we added the primary variable of interest (irAE or blood type) to obtain the final Cox-proportional hazards models:

$$\text{TTF} \sim \text{irAE} + \text{Age} + \text{Treatment type} \quad (1)$$

$$\text{TTF} \sim \text{Blood type} + \text{Age} + \text{Treatment type} \quad (2)$$

A secondary analysis stratified by blood type was pre-planned to investigate the association between TTF and irAE, in the case that both of the associations of irAE and blood type with TTF proved to be significant in the primary analysis:

$$\text{TTF} \sim \text{irAE} + \text{Age} + \text{Treatment types (within type O blood)} \quad (3)$$

$$\text{TTF} \sim \text{irAE} + \text{Age} + \text{Treatment types (within type A/B/AB blood)} \quad (4)$$

As sensitivity analysis to the secondary analysis, we used model (5) which included the main effects of irAE and blood type, their interaction, and selected confounders as predictors. The association of irAE with TTF among blood type A/B/AB was based on the test of irAE, and the association of irAE with TTF among blood type O was based on the test of both irAE and the interaction.

$$\text{TTF} \sim \text{irAE} + \text{Blood type} + \text{irAE} * \text{Blood type} + \text{Age} + \text{Treatment types} \quad (5)$$

Other sensitivity analyses included: (1) using Kaplan-Meier plots and the log-rank test to check the similarity of TTF among type A, B, and AB blood; (2) using all treatment regimens (more than one regimen for some patients); (3) repeating the same methods for those patients with primary cancer site skin, lung, or head and neck (n = 63), as these are the tumor types with the most historical data regarding response to ICB. Survival estimates and curves were computed with functions "survfit" and "survdiff" in package "survival"[17] in R (3.6.0).[18]

Results

Sample Characteristics

Of 241 patients who were identified as using immunotherapy during the study period, 107 subjects had blood type information available and had consented for data to be used for this analysis. Ages ranged from 28 years to 91 years (mean 58.5 years). Over half (55.1%) were male. The majority race/ethnicity was Caucasian (69.2%), with 4.7% Asian, 8.4% Black, and 17.8% Hispanic. Cancer types were as follows: skin (n = 15), lung (n = 23), head and neck (n = 25), and other (n = 44; including breast (n = 6), endocrine (n = 3), genitourinary (n = 4), GI (n = 19), GYN (n = 7), heme (n = 2), neuro (n = 1), and soft tissue (n = 2)). We used the first treatment regimen recorded in the medical record for each patient in the primary analysis. Immune therapy types included anti-CTLA-4 therapy for n = 13 subjects, anti-PD-(L)1 therapy for n = 93 subjects (anti-PD1 only (n = 75), anti-PD-L1 only (n = 16), anti-PD1 and anti-PD-L1 (n = 2)), and anti-PD(L)1-containing combination therapy (including other ICB, chemotherapy, or targeted agents) for n = 44 subjects. More than one therapy type might be included in a treatment regimen. Forty-four patients (41%) had type O blood, 41 (38%) had type A blood, 5 (5%) had type AB blood, and 17 (16%) had type B blood. Of the 107 patients, irAEs occurred in 44 (41%). Half of those with type O blood experienced irAEs, and the proportion was around one-third for those with type A/B/AB blood. Time to treatment failure was observed for 96 patients, with the remaining 11 censored. A descriptive summary of irAEs is included in Supplementary Table S1. No significant difference between regimens was observed for any covariates between patients with type O blood and type A/B/AB blood (Table 1).

Association of irAEs with TTF

Patients who experienced an irAE were observed to have longer TTF than those with no irAEs (Fig. 1; log-rank test, P = .003). In multivariable Cox regression, gender, race/ethnicity, and cancer site were excluded from the list of confounders after Backward selection (P > .30). The final model was adjusted for age and type of ICB treatment; patients experiencing an irAE had significantly longer TTF than those without an irAE (adjusted hazard ratio (aHR): 0.52; 95%CI 0.33 to 0.82).

Table 1. Sample characteristics according to blood type, type O vs type A/B/AB blood.

	Type O blood (n = 47)	Type A/B/AB blood (n = 73)	P-value
	Mean (95% CI)	Mean (95% CI)	
Age	59.5 (55.7, 63.2)	57.9 (54.7, 61.1)	.53
Gender			
Male	52.3% (37.5%, 67.0%)	57.1% (44.9%, 69.4%)	.76
Female	47.7% (33.0%, 62.5%)	42.9% (30.6%, 55.1%)	
Race/ethnicity			
Asian	2.3% (0%, 6.7%)	6.3% (0.3%, 12.4%)	.55
Black	11.4% (2.0%, 20.7%)	6.3% (0.3%, 12.4%)	
Hispanic	20.5% (8.5%, 32.4%)	15.9% (6.8%, 24.9%)	
Non-Hispanic White	65.9% (51.9%, 79.9%)	71.4% (60.3%, 82.6%)	
Histology			
Skin	15.9% (5.1%, 26.7%)	12.7% (4.5%, 20.9%)	.88
Lung	18.2% (6.8%, 29.6%)	23.8% (13.3%, 34.3%)	
Head and neck	25.0% (12.2%, 37.8%)	22.2% (12.0%, 32.5%)	
Others	40.9% (26.4%, 55.4%)	41.3% (29.1%, 53.4%)	
Treatment			
Anti-PD-(L)1 therapy	88.6% (79.3%, 98.0%)	85.7% (77.1%, 94.4%)	.88
Anti-PD-(L)1 -combination	34.1% (20.1%, 48.1%)	46.0% (33.7%, 58.3%)	.30
CTLA_4 therapy	11.4% (2.0%, 20.7%)	12.7% (4.5%, 20.9%)	1.00
IRAE			
Marked	50.0% (35.2%, 64.8%)	34.9% (23.1%, 46.7%)	.17

Anti-PD-(L)1 includes PD1-INHIBITOR and PD-L1-INHIBITOR; PD-combination includes targeted-therapy and CHEMO therapy.
P-value is from a 2 sample T test for the difference of age in 2 groups of interest; chi square test for testing the difference of other covariates in 2 groups of interest.
Abbreviations: CI, confidence interval.

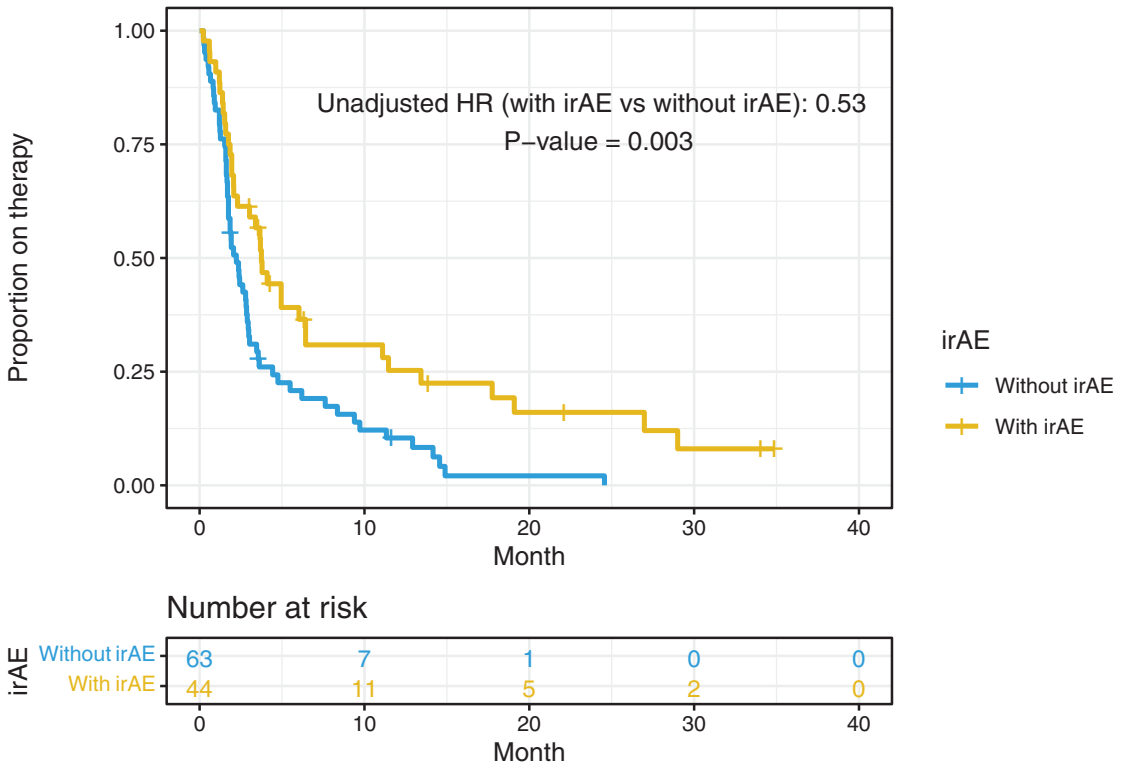

Figure 1. Time to treatment failure under treatment with ICB, comparing treatment regimens with and without irAEs.
Abbreviations: ICB, immune checkpoint blockade; HR, hazard ratio; irAE, immune-related adverse events. irAE = 0 if no immune-related adverse events occurred during the treatment regimen and irAE = 1 otherwise. *P*-value from log-rank test, and $P < .05$ indicates a statistically significant difference.

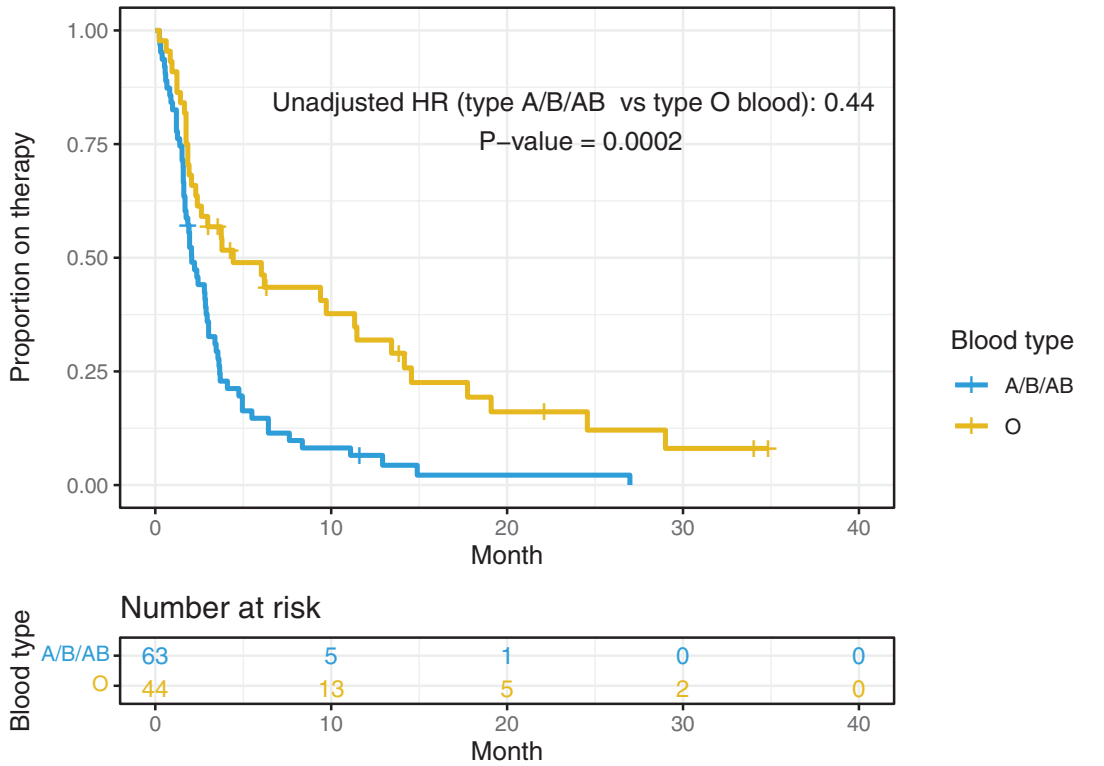

Figure 2. Time to treatment failure under treatment with ICB, type O blood compared with type A/B/AB blood.
Abbreviations: ICB, immune checkpoint blockade; HR, hazard ratio. *P*-value came from log-rank test, and $P < .05$ indicates the statistically significant difference.

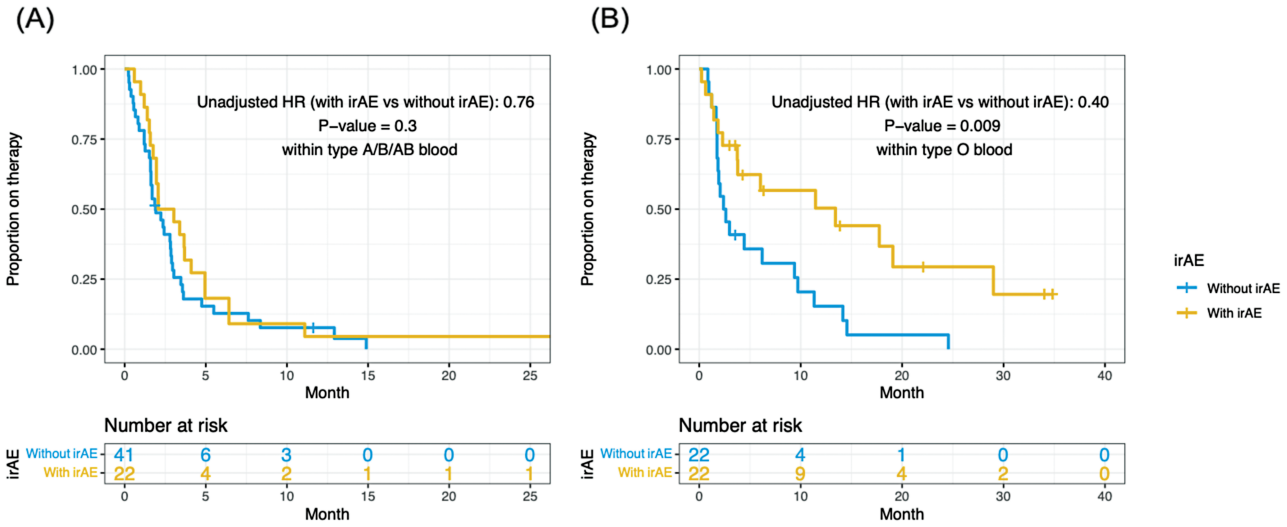

Figure 3. Time to treatment failure under treatment with ICB, comparing treatment regimens with and without irAEs, (**A**) within type O blood and (**B**) type A/B/AB blood, respectively.
Abbreviations: ICB, immune checkpoint blockade; HR, hazard ratio. *P*-value came from log-rank test, and $P < .05$ indicates the statistically significant difference.

Association of Blood Type with TTF and with irAEs

For those with type O blood, 50.0% of patients experienced least one irAE, and the proportion of patients with an irAE was 34.9% for those with type A/B/AB blood ($P = .17$, Pearson's chi-squared test). Type O blood was associated with longer TTF when compared with type A/B/AB blood (Fig. 2; log-rank test, $P = .0002$). Adjusted Cox regression models again included age and type of ICB treatment, and indicated that patients with type O type had an adjusted hazard ratio of 0.50 (aHR: 95% CI 0.32 to 0.78) compared with those with type A/B/AB blood, indicating longer TTF. There was no evidence for a difference in TTF among the A, B, and A/B blood types (Supplementary Fig. S1).

Association Between irAEs and TTF, Stratified by Blood Type

Figure 3A shows TTF of type O blood, stratified by the presence or absence of irAEs; Fig. 3B shows the same for A/B/AB type. In adjusted Cox regression models including age and type of ICB treatment, for those with type O blood, the aHR was 0.41 (95%CI: 0.18 to 0.96) comparing patients with to those without irAEs. Within type A/B/AB blood, irAEs was not significantly related to TTF (aHR: 0.69, 95%CI: 0.39 to 1.21), suggesting that irAEs may be a biomarker of improved response, but only for those with type O blood. Among those with type O blood and irAEs, median TTF was 13.4 months (95% CI: 3.79, NA), compared with less than 2.55 months (95% CI: 1.95, 4.95) for other patients. The results of the sensitivity analyses using the combined data with an interaction term in the model were consistent with the results of the stratified analysis: presence of irAEs itself was not significant (0.67, 95% CI: 0.39 to 1.17); however, the irAE and its interaction with blood type were significant, for the outcome TTF (chi-square test, 2 df, P .01). Results for other sensitivity analyses are included in Supplementary Appendixes 1, 2, Figs. S2-S7.

Discussion

Our analysis of patients with cancerat our institution who received immunotherapy and had blood type information available from 1/2014 to 12/2018 indicates that patients with type O blood had substantially improved TTF after ICB compared to those with type A/B/AB blood. In addition, considering only patients with type O blood, those who developed irAEs had improved TTF compared with those without irAEs. However, for patients with type A/B/AB blood, there was no difference in TTF according to the presence or absence of irAEs; the association of irAEs with longer TTF was seen only among those with type O blood. This was true in unadjusted analyses, and also in analyses adjusted for age and type of immunotherapy. Time to treatment failure did not differ appreciably by cancer site or gender. The majority of our patients received anti-PD-(L)1 blockade as therapy, although patients receiving combination therapy with ICB and chemotherapy or targeted therapy, and other immunotherapy were included in our analysis.

In the US, type O blood represents about half of the population, across multiple ethnic groups,[19] similar to the 41% prevalence observed in our data. Patients with type O blood lack RBC surface antigens,[3] and thus we speculate that they may potentially have a broader T-cell repertoire available for immune checkpoint inhibitors to effectuate against cancer cells. Over time, cancers may evolve to preferentially select for neoantigens that appear to the immune system to resemble blood proteins, as such proteins are a functional blind spot in the T-cell repertoire,[13] similar to HLA-specific effects as have been described.[2,20] Alternatively, the presence of anti-A and anti-B antibodies in the plasma of type O blood patients could prime an immune response (for therapeutic efficacy or irAE toxicity), although this mechanism for potential immune activation has not been as well described as T-cell-specific effects.[21]

The magnitude of benefit associated with type O blood and irAEs seen in our study was substantial. Among patients with type O blood and irAEs, median TTF was over 13 months, compared to less than 3 months for other patients. The estimated effect sizes in our study on heterogenous patients with metastatic solid tumors were greater than those associated with improved OS seen for HLA genotypes in cohorts of melanoma and patients with non-small cell lung cancer.[2] While these studies used different outcomes and studied different

patient populations, our results are consistent and indicate that genetic haplotypes associated with blood type may also be an important factor in determining mechanisms of benefit from ICB, and in identifying patient populations which may be good candidates for this type of immune-directed therapy.

Multiple sensitivity analyses confirmed our findings for these patients who received multiple regimens of immunotherapy. Our analysis also indicates that the association of irAEs with longer TTF is not simply an artifact of longer time on treatment, as no such association was seen for irAE's among patients with A/B/AB blood. Limitations of the study include the heterogeneity of tumor types and combinations of therapies assessed, and that the number of prior lines of systemic treatment was not available in our data. However, we note that blood type is likely not strongly associated with these potential confounders, given its assignment by Mendelian randomization, and also that no robust association of blood type with tumor type, chemotherapy and/or targeted therapy, or number of lines of therapy, has been described that we are aware of. Similarly, no association between lines of therapy or tumor type and presence of irAEs has been described that we are aware of. Thus, although several of these potential confounders may be associated with the outcome TTF, they are unlikely to strongly confound the relation between our exposures of interest and TTF. In addition, we have adjusted for the heterogeneity from different immunotherapies and tumor types as well as chemotherapy by adding these factors as explanatory variables in our analyses, although residual confounding after fitting multivariable statistical models always remains a possibility. The majority of our patients had metastatic melanoma, lung, or head and neck tumors and samples were collected from a US academic medical center population, which may not be representative of other locales that utilize cancer immunotherapy.

Our data are hypothesis generating; future investigation in independent data sets is needed to confirm our findings. Validation studies could include using existing immunotherapy whole-exome datasets with imputed ABO blood type, and also larger prospective patient series. Additionally, further exploration of the grade of irAE and requisite immunosuppression and its relationship to blood type would be of interest. If confirmed, these findings might support investigation of future therapeutic strategies to overcome blind spots in the T-cell immune repertoire.

Conclusion

The results of this retrospective study of a cohort of patients receiving ICB suggests there is a preferential benefit for patients with type O blood, and, in particular, for those patients with type O blood who developed irAEs. If validated, these findings may support investigation of future therapeutic strategies to overcome blind spots in the T-cell immune repertoire.

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Conflict of Interest

Sandip Patel: AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Illumina, Rakuten, Paradigm, Tempus (C/A), Bristol-Myers Squibb, Eli Lilly, Incyte, AstraZeneca/MedImmune, Merck, Pfizer, Roche/Genentech, Xcovery, Fate Therapeutics, Genocea, Iovance (RF—inst). The other authors indicated no financial relationships.

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Author Contributions

Conception/design: S.P. Provision of study material/patients: S.P. Collection and/or assembly of data: S.P., K.H. Data analysis and interpretation: R.C., K.M., X.Z. Manuscript writing: S.P., K.M., R.C., X.Z. Final approval of manuscript: All authors.

Data Availability

The data can be found in public repository: https://www.openicpsr.org/openicpsr/project/141261/version/V1/view

Supplementary Material

Supplementary material is available at *The Oncologist* online.

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