ROS1 single nucleotide variants predict favorable survival outcomes on immunotherapy regimens in non-small cell lung cancer

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Background

Only a fraction of non-small cell lung cancer patients who receive immune checkpoint inhibitor (ICI) treatment will respond, largely because current FDA-approved biomarkers still leave room for improvement to identify more responders. We hypothesized that modeling the time-dependent interaction between treatment and tumor genetics may reveal novel associations. We further hypothesized that real-world data (RWD), as opposed to clinical trial data, may contain these associations, as RWD possesses a potentially more diverse patient population and time-to-event treatment history across the diverse regimens used in routine clinical practice.

Method

We examined the relation between tumor genetics, treatment, and real-world progression-free survival (PFS) in two RWD cohorts (Tempus discovery cohort, n = 1458; Dana Farber Cancer Institute Profile independent validation cohort, n = 466) by utilizing a Cox proportional hazards model with a time-dependent covariate for whether a patient was receiving an ICI-containing treatment regimen. Specifically, we included an indicator variable that denoted whether an individual was receiving an ICI regimen (=1) or not (=0), and enumerated the time intervals associated with each treatment status. We performed a univariate analysis for each mutated gene from tumor sequencing, and included a gene-treatment interaction term to permit identification of genes that were predictive (i.e. specific to a treatment) rather than prognostic. Our model included additional covariates to control for known predictive (tumor mutation burden[TMB]) and prognostic factors (age, sex).

The analysis model is as follows:

$$h(t) = h_0(t)\exp(\beta_0 X + \beta_1 T(t) + \beta_2 X * T(t) + \sum_c C_i \beta_{C_i}$$

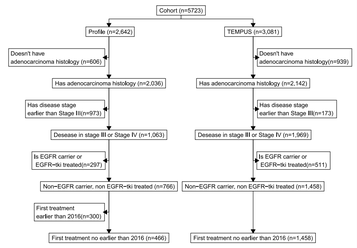
C : {age, sex, smoking status, TMB}
X : gene being tested
$T(t)$: a time-dependent covariate indicating ICI treatment status

Results

Cohort demographics and study inclusion criteria

	TEMPUS (N=3081)	Profile (N=2642)
Ever on ICI, N (%)	2371(76.9)	1251(47.3)
Age, N (%)		
<65y	1390(54.9)	1008(38.2)
>=65	1691(45.1)	1002(37.9)
missing		631(23.1)
Sex, N (%)		
Male	1574(51.1)	1097(41.5)
Female	1507(48.9)	1545(58.5)
Histology, N (%)		
has adenocarcinoma	2142(69.5)	2036(77.1)
none-adenocarcinoma	939(30.5)	606(22.9)
First ICI(+x) line, N (%)*		
1	1769(74.6*)	721(57.6*)
2+	602(25.4*)	530(42.4*)
Stage, N (%)		
less than Stage 3	120(3.9)	500(18.9)
Stage 3	614(19.9)	317(12.0)
Stage 4	2244(76.2)	1037(39.3)
missing		865(32.7)
Smoker, N (%)		
No	1286(41.7)	NA
Yes	1795(58.3)	NA
Key gene prevalence, N (%)		
STK11	393(12.8)	410(15.5)
KEAP1	461(15.0)	389(14.7)
ROS1	155(5.0)	180(6.8)

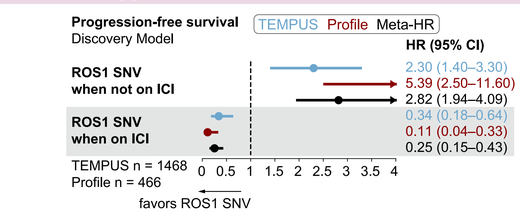
*out of samples ever on ICI

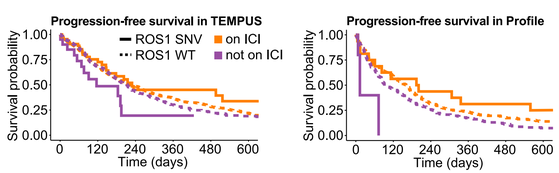


Cohort demographics (age, sex, smoker), clinical (histology subtype, line of ICI treatment, disease stage) and genomic profiles (key gene mutation prevalence).

CONSORT diagram depicting criteria used to select patients for this study. Additional filtering on patient enrollment time was required for Profile.

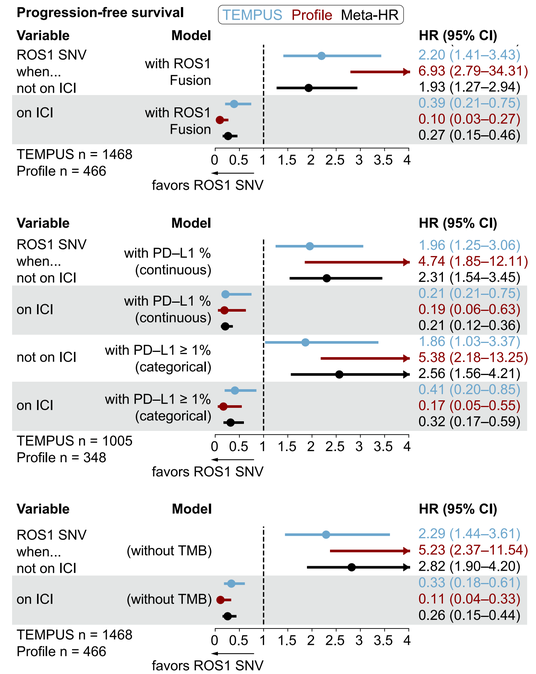
ROS1 SNV significantly associated with favorable PFS on ICI therapy





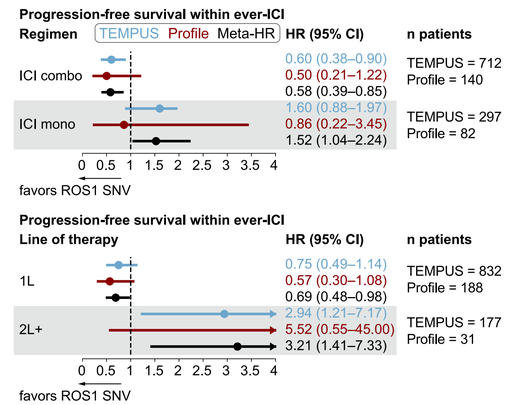
In the discovery cohort (TEMPUS), we identified a significant association between ROS1 single nucleotide variation (SNV) and favorable PFS on ICI versus non-ICI treatment. This association replicated in an independent validation cohort (Profile). KM curves represent simplified ROS1 SNV effect on ICI versus non-ICI treatment in TEMPUS and Profile.

ROS1 SNV association with favorable PFS is distinct from ROS1 fusion, PD–L1, and TMB



In both the discovery (TEMPUS) and validation (Profile) cohorts, and overall (Meta-HR), the hazard ratio of ROS1 SNV on ICI and not on ICI is robust to addition of ROS1 fusion[1] (for which individuals are typically treated with TKI), PD-L1[2] status or removal of TMB[3] in the model. This importantly showed that the association of ROS1 SNV with favorable PFS on ICI therapy is independent of these other biomarkers.

ROS1 SNV association with favorable PFS is specific to regimen and line of therapy



Across both cohorts, ROS1 SNV association with favorable PFS was specific to those receiving an ICI combination regimen, as opposed to monotherapy. Additionally, this effect was specific to those patients treated with ICIs in a first-line setting.

Conclusions

By utilizing the large-scale real-world dataset, TEMPUS, and employing a model with a time-dependent covariate for ICI treatment, we identified an association between ROS1 SNVs and favorable PFS specific to ICI treatment. This association is validated in an independent real-world dataset Profile.

ROS1 SNV was independent of common pre-existing predictive biomarkers for ICIs, namely TMB and PD–L1 status. The favorable ROS1-PFS association was also not explained by ROS1 fusion.

Because this association was specific to the first-line ICI setting, our finding may clarify ICI usage where clinical practice for ICI treatment is still evolving.

Declaration of interests: YW, KCB, EJ, GJS are current employees of AstraZeneca with stock ownership, interests, and/or options in the company. SCP is a former employee of Tempus with stock ownership, interests, and/or options in the company.

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Presented at the AACR 2025, Chicago, 28 April 2025

Supported by AstraZeneca