Immunotherapy-mediated thyroid dysfunction: genetic risk and impact on outcomes with PD-1 blockade in non-small cell lung cancer

SUPPLEMENT

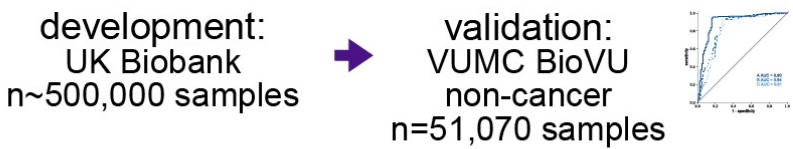**Table of Contents**

Supplementary Figure 1

(1) Evaluation of impact of thyroid irAEs on outcomes to PD-1 blockade therapy

MSK cohort
n=551
+
VUMC cohort
n=193

CPI cohort ➡

(2) Derivation of spontaneous hypothyroidism PRS

development:
UK Biobank
n~500,000 samples

➡

validation:
VUMC BioVU
non-cancer
n=51,070 samples

hypothyroid
polygenic risk score (PRS)

(3) Assessment of PRS in predicting thyroid irAEs in patients who received PD-1 blockade therapy

test:
CPI cohort

replication:
DFCI cohort
n=561

Supplementary Figure 1. Schema of the methods for examining the relationships between spontaneous hypothyroidism, thyroid irAEs, and response to anti-PD-1 therapy.

Supplementary Figure 2

Supplementary Figure 2. Thyroid irAEs as a predictor of PFS and OS in individuals with OS > 90 days in the MSK cohort. Kaplan-Meier survival curves are unadjusted and compare those who had a thyroid irAE to those who did not have a thyroid irAE. The x-axis reflects time from start of CPI therapy.

Supplementary Figure 3

A

B
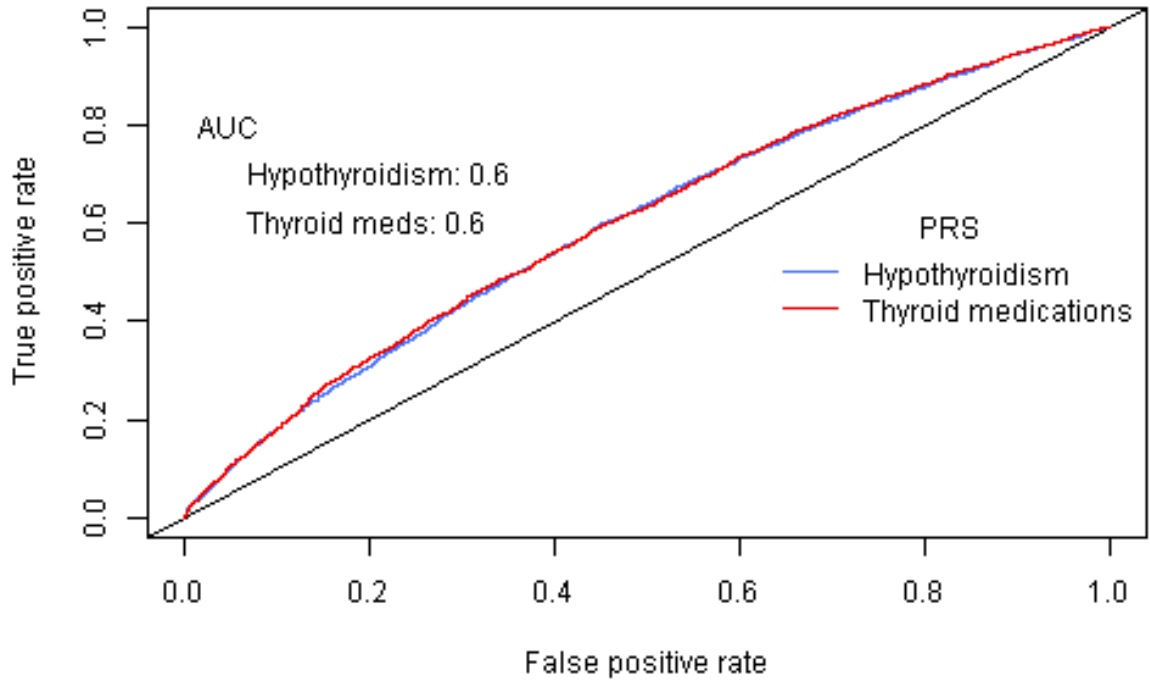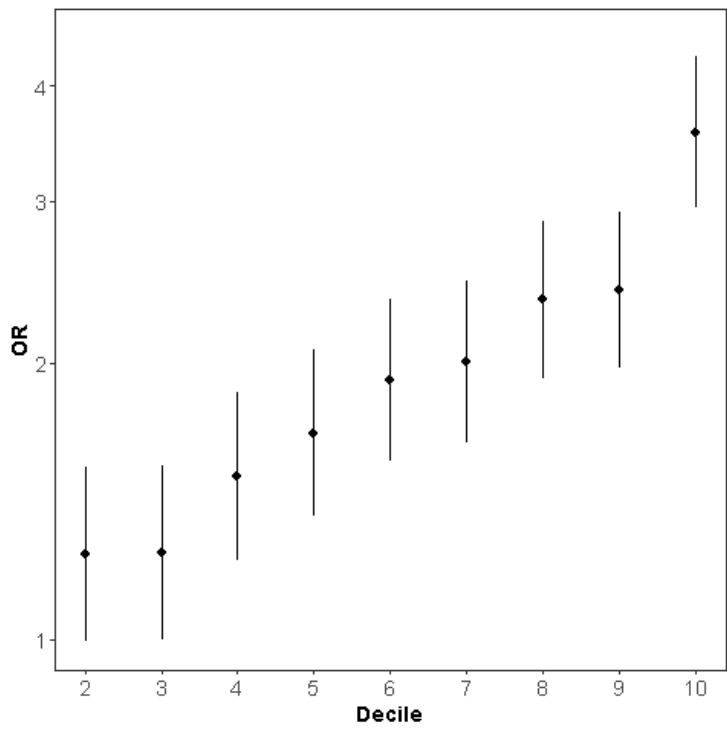
Supplementary Figure 3. Validation of PRS models for thyroid disease developed in UK Biobank in BioVU. ROC curves for PRS for self-reported hypothyroidism and taking thyroid medications were developed in UK Biobank using LDpred and tested in BioVU among participants who were not known to have lung cancer and received CPI. B. Relative risk of PRS by decile in the non-cancer VUMC BioVU cohort.

Supplementary Figure 4

Thyroid Medication PRS
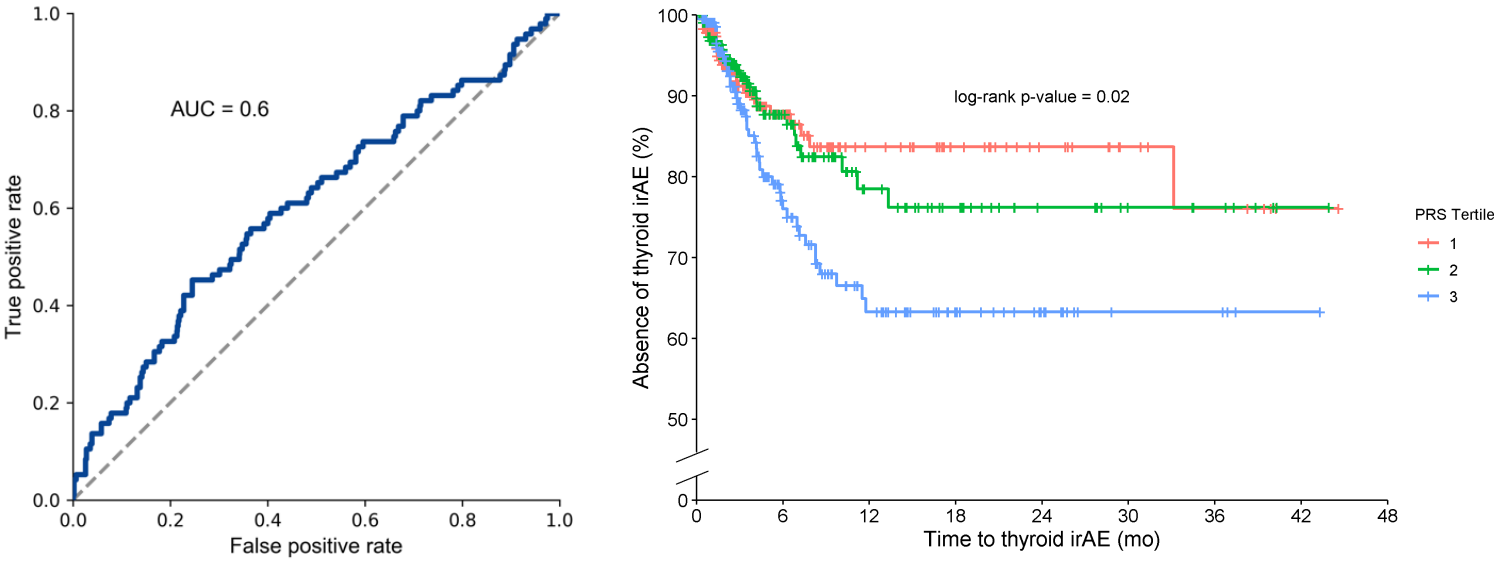
Supplementary Figure 4. Hypothyroidism PRS (using thyroid medication PRS) as a predictor of CPI-induced hypothyroidism events in the VUMC and MSK cohort. The left panel shows the ROC curve and right panel shows time to event by PRS tertile. P-values for the three curves are calculated using a log-rank test.

Supplementary Figure 5

A

B
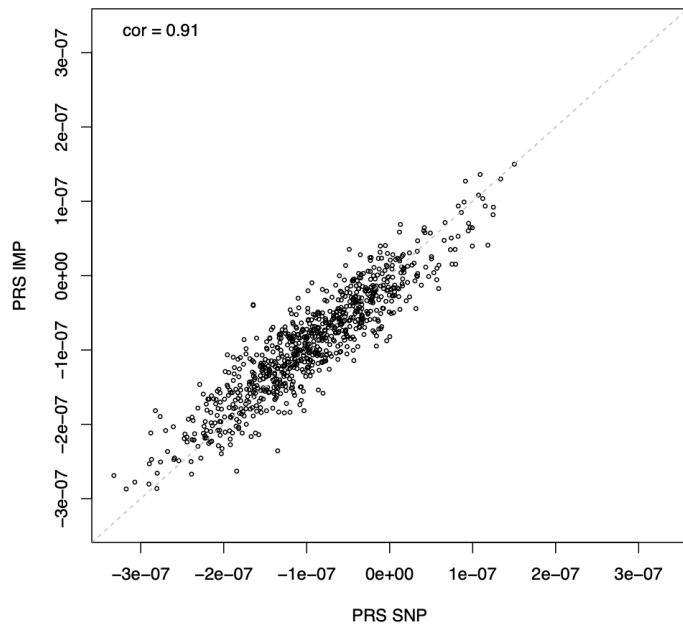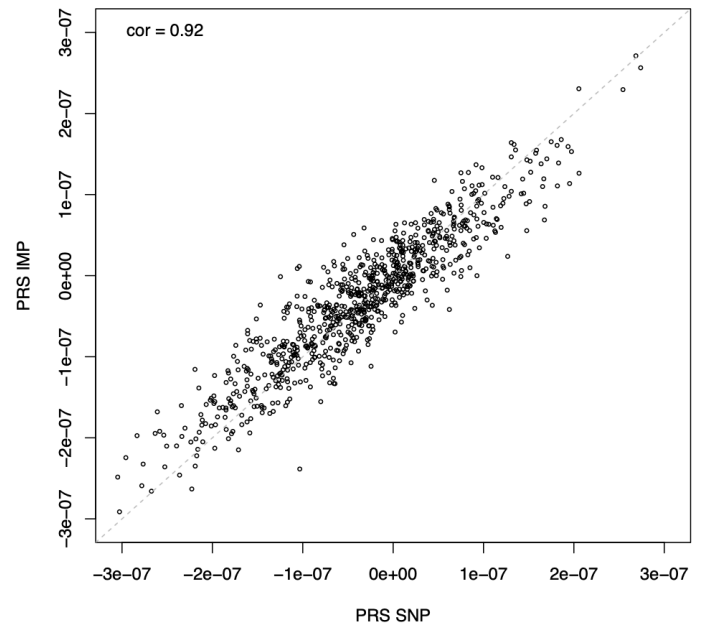
Supplementary Figure 5. PRS values for DFCI tumor imputed and germline genotyped samples. PRSs shown are: (A) hypothyroidism and (B) thyroid medication. Each point represents an individual with genotyped (x-axis) and imputed (y-axis) PRS values. Pearson correlation between the scores is listed in each panel.

Supplementary Figure 6

Thyroid Medication PRS
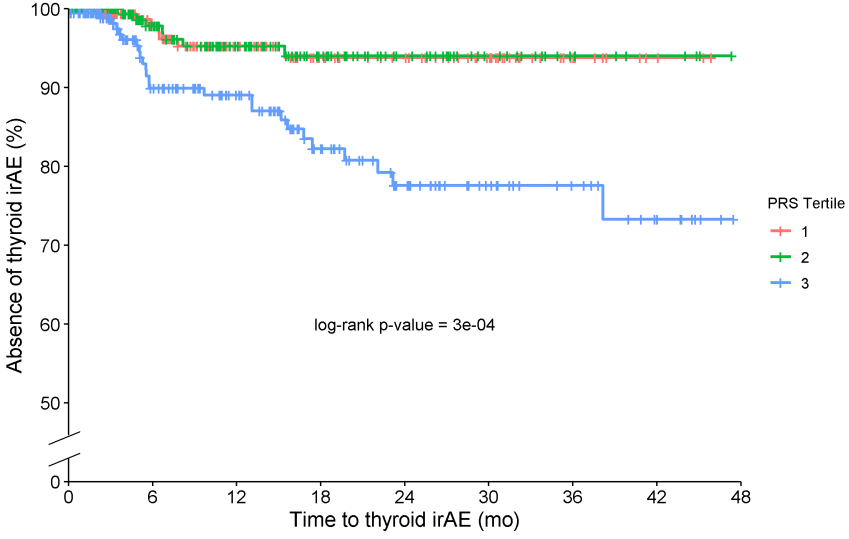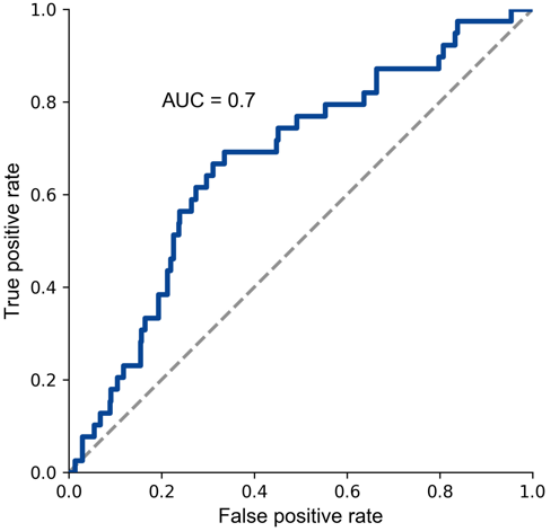
Supplementary Figure 6: Hypothyroidism PRS (using thyroid medication PRS) as a predictor of CPI-induced hypothyroidism events in the DFCI cohort. The left panel shows the ROC curve and right panel shows time to event by PRS tertile. P-values for the three curves are calculated using a log-rank test.

Supplementary Figure 7

A

B
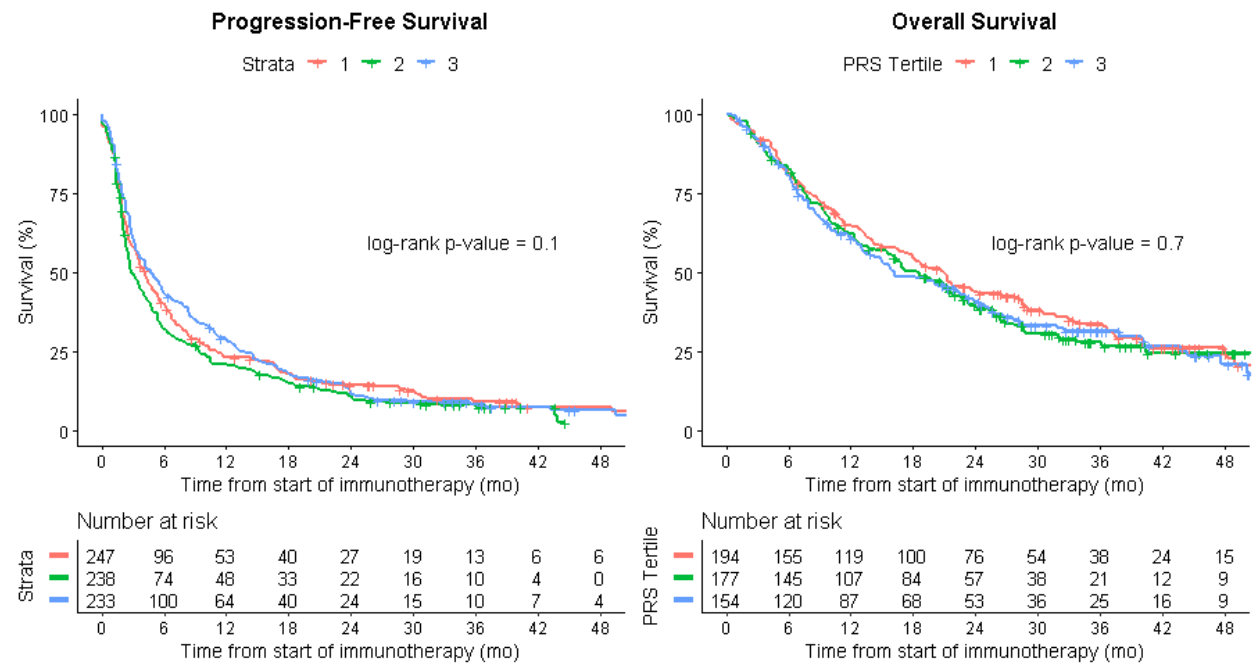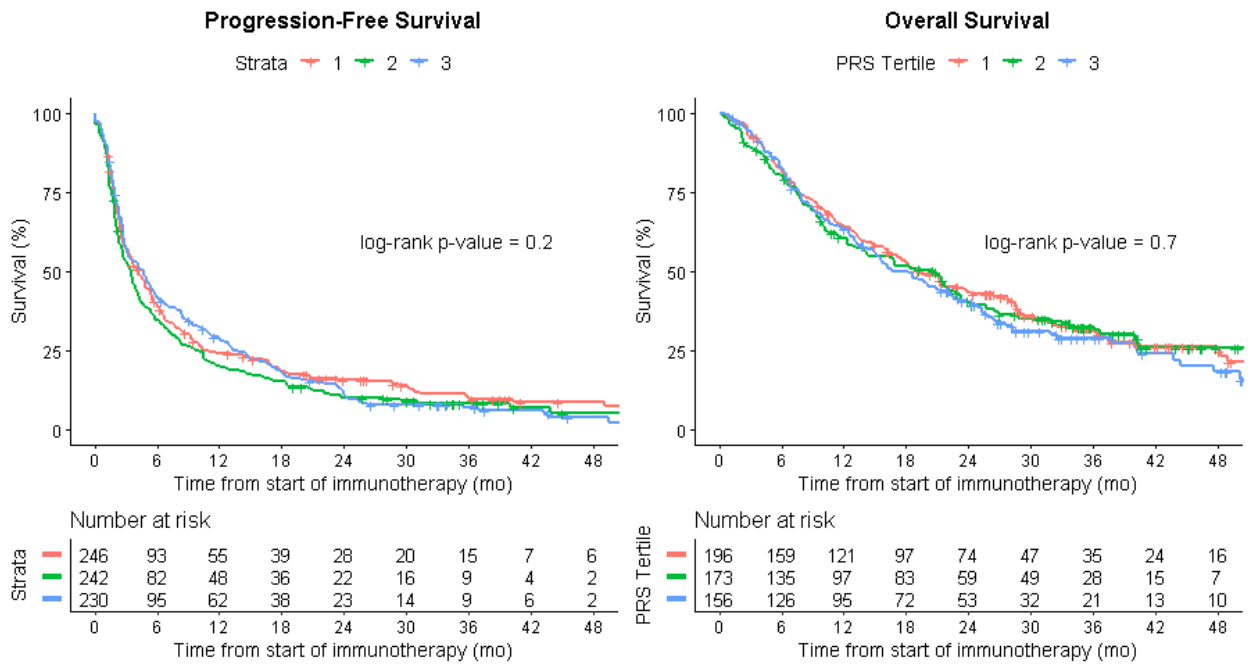
Supplementary Figure 7. PFS in the combined MSK + VUMC cohort and OS in the MSK cohort starting from the time of CPI therapy start by PRS tertile. (A) hypothyroidism PRS and (B) thyroid medication PRS

Supplementary Table 1. Individual SNPs from the UK Biobank hypothyroidism GWAS that were associated with CPI-induced thyroid irAEs in the MSK + VUMC cohort at p < 0.05. Bold italics indicates variant passed multiple hypothesis testing. Effect and alternate alleles in the MSK + VUMC cohort were aligned to the effect and alternate alleles in the original UK Biobank GWAS. Models in the MSK + VUMC cohort were adjusted for age at diagnosis, sex, and the first ten principal components.

Chr: chromosome, SNP: single nucleotide polymorphism, Alt allele: alternate allele, freq: frequency, HR: hazard ratio, L95: lower 95% confidence interval, U95: upper 95% confidence interval

| Variant Information					MSK + VUMC Cohort Results					UK Biobank GWAS Results			
Chr	Position (GRCh37)	SNP	Effect allele	Alt allele	Effect allele freq	HR	L95	U95	p-value	Effect allele freq	β	standard error	p-value
6	32379295	rs9268515	G	C	0.86	0.5	0.35	0.71	1.12E-04	0.81	-0.00519	0.000883	2.80E-09
16	67973953	rs5923	G	A	0.93	0.45	0.28	0.72	8.80E-04	0.95	-0.00574	0.001039	2.60E-08
16	67476572	rs8056260	A	G	0.91	0.43	0.25	0.72	1.37E-03	0.96	-0.00704	0.001075	3.80E-11
8	141639262	rs11783023	C	T	0.26	1.62	1.19	2.21	2.09E-03	0.28	0.003325	0.000491	1.20E-11
16	68361498	rs7206600	C	T	0.96	0.41	0.23	0.73	2.41E-03	0.98	-0.00807	0.001454	2.60E-08
2	204769395	rs28386480	C	T	0.52	1.55	1.15	2.1	3.72E-03	0.54	0.002749	0.000442	6.60E-10
6	32608931	rs9272679	T	C	0.76	1.76	1.2	2.57	3.77E-03	0.43	-0.00992	0.000665	5.80E-50
6	32587350	rs1281932	G	A	0.81	0.62	0.45	0.86	4.68E-03	0.8	-0.00974	0.000792	1.40E-34
20	17860022	rs6111715	G	C	0.81	0.61	0.43	0.86	4.87E-03	0.82	0.003711	0.000576	7.80E-11
2	204698111	rs2882970	T	C	0.74	1.7	1.17	2.48	5.53E-03	0.75	0.005722	0.000518	8.70E-29
1	200840467	rs12756886	T	C	0.89	0.56	0.37	0.85	6.01E-03	0.88	-0.00437	0.00068	9.40E-11
6	32633282	rs9274447	T	C	0.79	1.83	1.19	2.81	6.15E-03	0.66	-0.00775	0.00069	1.80E-28
4	10716939	rs4293777	G	C	0.53	0.66	0.49	0.89	6.23E-03	0.53	-0.0037	0.000442	7.80E-17
16	68390697	rs61733486	C	T	0.94	0.5	0.3	0.83	7.28E-03	0.94	-0.00521	0.000946	2.30E-08
6	29367498	rs4713220	A	T	0.56	1.52	1.12	2.06	7.31E-03	0.57	0.003625	0.000654	2.60E-10
12	111582630	rs73413596	T	C	0.87	0.56	0.37	0.86	7.86E-03	0.92	0.00514	0.000839	3.10E-10
11	116979911	rs12271161	G	A	0.78	1.83	1.17	2.86	7.88E-03	0.81	0.003652	0.000559	3.10E-11
6	31437566	rs9404989	G	T	0.98	0.32	0.14	0.74	8.22E-03	0.98	0.013439	0.001705	2.50E-14
7	37382465	rs60600003	T	G	0.9	0.56	0.36	0.86	8.24E-03	0.9	-0.0044	0.000739	9.30E-10
6	31312058	rs2394977	C	G	0.58	0.68	0.51	0.91	1.04E-02	0.56	0.004264	0.000653	1.00E-15
6	31463128	rs9267352	G	A	0.74	0.66	0.47	0.91	1.14E-02	0.74	0.005833	0.000676	7.20E-16
6	31616174	rs569347663	A	T	0.97	0.44	0.24	0.84	1.20E-02	1	-0.0354	0.005556	1.60E-10
2	1378060	rs4927602	G	A	0.49	0.69	0.51	0.93	1.36E-02	0.5	-0.00264	0.000467	2.40E-08
3	188070964	rs2103022	A	G	0.23	1.53	1.09	2.15	1.41E-02	0.24	0.002904	0.000527	1.40E-08
14	98692996	rs1257926	G	A	0.53	0.7	0.53	0.94	1.59E-02	0.52	-0.00278	0.000443	1.10E-10
6	32605295	rs1129735	C	T	0.66	0.7	0.52	0.94	1.67E-02	0.63	-0.00923	0.0007	8.00E-41

6	31435869	rs4713466	C	T	0.89	0.62	0.42	0.92	1.71E-02	0.86	0.005798	0.000943	3.10E-09
6	31436047	rs2518028	T	C	0.32	0.66	0.47	0.93	1.73E-02	0.35	0.005452	0.000708	8.90E-19
14	68749927	rs3784099	G	A	0.67	1.5	1.07	2.11	1.77E-02	0.72	0.003107	0.000491	2.70E-11
1	108379684	rs2125748	G	A	0.77	1.57	1.08	2.28	1.89E-02	0.75	0.002831	0.000512	1.80E-08
6	32587588	rs9271406	A	G	0.56	0.71	0.54	0.95	2.08E-02	0.5	-0.00606	0.000686	4.60E-23
17	7240391	rs61759532	C	T	0.83	0.69	0.5	0.94	2.11E-02	0.75	-0.00399	0.000527	1.00E-14
6	32580591	rs7449585	G	T	0.74	0.7	0.52	0.95	2.12E-02	0.95	0.010027	0.001139	1.60E-20
6	32624377	rs567302488	G	A	0.93	3.19	1.19	8.59	2.15E-02	0.62	-0.00888	0.000693	1.70E-37
6	31247441	rs2844607	C	T	0.78	0.69	0.5	0.95	2.27E-02	0.72	0.005255	0.000684	1.30E-10
9	21637351	rs71504798	C	G	0.92	3.11	1.17	8.26	2.28E-02	0.91	-0.00499	0.000767	8.20E-11
11	117030633	rs200545029	T	C	0.94	2.75	1.15	6.59	2.34E-02	0.94	0.006043	0.000953	8.60E-11
6	32078373	rs3807039	A	C	0.92	0.61	0.39	0.94	2.36E-02	0.89	-0.00487	0.000805	2.20E-08
3	105911539	rs7633167	C	A	0.44	0.71	0.53	0.96	2.37E-02	0.43	0.002601	0.000448	5.70E-09
1	108337108	rs17484960	G	A	0.55	0.72	0.54	0.96	2.38E-02	0.5	-0.00312	0.000441	9.00E-13
1	236629134	rs12117927	C	A	0.54	0.71	0.53	0.96	2.52E-02	0.51	-0.00267	0.000452	1.10E-09
6	32402889	rs9268615	G	A	0.55	0.72	0.55	0.96	2.55E-02	0.64	-0.0069	0.000848	1.10E-15
19	7240776	rs4804433	G	T	0.25	1.42	1.04	1.93	2.56E-02	0.21	0.00325	0.00054	5.80E-09
6	32603321	rs62404084	C	T	0.84	0.66	0.45	0.95	2.71E-02	0.81	0.005054	0.000717	6.40E-10
3	12195622	rs308952	A	G	0.14	0.52	0.3	0.93	2.75E-02	0.13	0.004684	0.000648	1.40E-13
3	188080043	rs7640386	T	C	0.75	0.68	0.48	0.96	2.78E-02	0.78	-0.00432	0.000532	2.00E-16
9	100506414	rs7862400	C	A	0.44	0.71	0.52	0.96	2.80E-02	0.53	-0.00331	0.000447	3.90E-14
9	100737755	rs10984601	A	G	0.74	0.71	0.52	0.96	2.88E-02	0.7	-0.00388	0.000491	1.50E-15
16	67349478	rs138453996	G	A	0.97	0.46	0.23	0.93	2.97E-02	0.98	-0.01041	0.001578	3.10E-11
6	29566369	rs3095273	A	G	0.26	0.67	0.47	0.96	3.00E-02	0.29	-0.00376	0.000667	3.00E-08
6	32781776	rs2856997	C	A	0.6	0.71	0.52	0.97	3.00E-02	0.61	0.003736	0.000577	1.60E-08
6	91024294	rs927297	G	C	0.35	1.39	1.03	1.86	3.04E-02	0.4	0.003524	0.000456	4.70E-15
9	5425847	rs10815220	A	G	0.75	1.47	1.04	2.09	3.09E-02	0.72	-0.00308	0.000491	4.80E-10
6	31850308	rs74434374	C	A	0.95	0.55	0.32	0.95	3.17E-02	0.95	0.008211	0.001318	2.30E-10
6	31249127	rs2253487	G	A	0.6	0.73	0.55	0.97	3.18E-02	0.59	0.004741	0.000632	2.00E-09
9	21585265	rs970987	C	A	0.37	0.69	0.49	0.97	3.33E-02	0.34	0.003916	0.000468	3.80E-17
2	204573392	rs35988305	C	G	0.62	1.38	1.02	1.87	3.59E-02	0.64	0.003279	0.000459	2.90E-13
6	31397689	rs143015185	A	T	0.96	0.53	0.3	0.96	3.61E-02	0.95	-0.01705	0.001288	5.30E-25
4	149648035	rs17583283	G	A	0.52	0.74	0.55	0.98	3.62E-02	0.56	0.00319	0.000446	3.50E-13
5	133455153	rs244693	A	C	0.07	1.66	1.03	2.67	3.64E-02	0.08	0.005357	0.000824	9.60E-11
10	63809624	rs10821948	C	A	0.62	0.73	0.55	0.98	3.77E-02	0.68	-0.00397	0.000474	1.20E-17
6	32667595	rs1794279	G	T	0.92	2.13	1.04	4.37	3.85E-02	0.87	-0.0141	0.001508	2.80E-19
6	32582603	rs13204736	G	T	0.65	0.74	0.55	0.99	3.94E-02	0.7	-0.00642	0.000762	3.00E-18
4	40307564	rs13136820	C	T	0.36	1.36	1.02	1.83	3.95E-02	0.32	0.002945	0.000475	8.90E-10
19	50197406	rs12981033	A	G	0.58	0.73	0.54	0.99	3.98E-02	0.61	0.00303	0.000452	7.00E-12
1	108321313	rs4914960	A	G	0.22	0.66	0.44	0.98	4.08E-02	0.19	-0.00421	0.00056	3.70E-14

4	149720635	rs13143096	C	T	0.5	0.74	0.55	0.99	4.14E-02	0.5	0.002441	0.000444	1.90E-08
8	8317887	rs2921059	G	T	0.95	0.56	0.32	0.98	4.19E-02	0.56	0.005286	0.000867	9.60E-10
16	79337033	rs2881665	C	T	0.16	1.5	1.01	2.22	4.22E-02	0.12	0.003754	0.000682	3.90E-08
12	112179471	rs4766897	T	C	0.29	1.36	1.01	1.83	4.22E-02	0.34	0.008059	0.000466	2.20E-68
2	204740866	rs231726	C	T	0.7	0.72	0.53	0.99	4.26E-02	0.67	-0.0087	0.00047	7.00E-77
6	31080859	rs2233966	A	G	0.46	1.35	1.01	1.81	4.26E-02	0.5	-0.00759	0.000764	7.30E-16
6	31403625	rs7759215	C	T	0.97	0.56	0.32	0.98	4.35E-02	0.87	-0.00919	0.000835	1.50E-21
6	32594470	rs114309058	G	A	0.49	1.35	1.01	1.8	4.54E-02	0.75	0.005841	0.000705	4.30E-16
17	7252148	rs2292067	G	T	0.65	0.73	0.54	0.99	4.57E-02	0.63	-0.00264	0.000461	5.70E-09
13	111206226	rs9521838	G	A	0.8	1.48	1.01	2.19	4.65E-02	0.77	0.002838	0.000525	4.80E-08
6	33047898	rs2567281	C	A	0.89	1.99	1.01	3.95	4.77E-02	0.92	0.006656	0.000861	6.70E-15
13	24789706	rs1220604	G	A	0.53	1.35	1	1.81	4.83E-02	0.55	-0.00267	0.000449	1.90E-09
9	21582326	rs7046475	T	C	0.22	0.66	0.43	1	4.87E-02	0.22	0.004	0.000537	7.60E-14
6	33048937	rs7770501	C	G	0.86	1.81	1	3.27	4.91E-02	0.88	0.006474	0.000764	8.20E-17
13	43063831	rs66749983	A	T	0.7	1.4	1	1.94	4.91E-02	0.69	-0.00361	0.000478	3.90E-14
6	31917291	rs2072634	C	T	0.98	0.49	0.24	1	4.98E-02	0.98	0.01083	0.001717	1.10E-09

Supplementary Table 2. PRS as a predictor of PFS in the combined MSK + VUMC cohort and OS in the MSK cohort. Time-dependent models were adjusted for age, sex, combined anti-PD-(L)1 + anti-CTLA-4 therapy, and first 10 principal components. Adjusted hazard ratios are per standard deviation of the PRS.

PRS Phenotype	PFS			OS		
	aHR	95% CI	p-value	aHR	95% CI	p-value
Hypothyroidism	1.00	0.92-1.08	0.96	1.05	0.94-1.18	0.4
Thyroid medications	1.00	0.92-1.08	0.97	1.07	0.96-1.20	0.2