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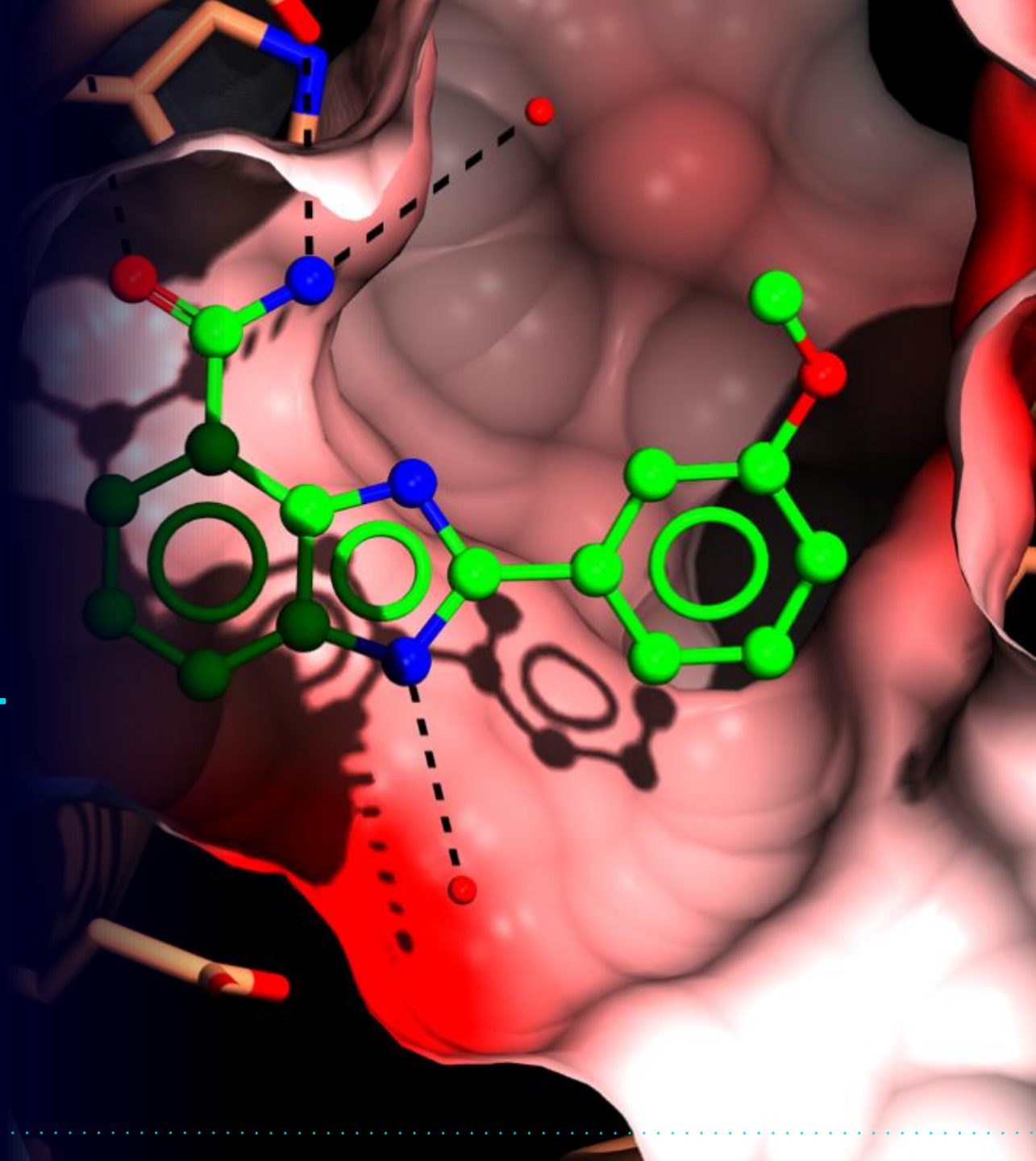
COX-2 SIGNATURE:

NOVEL PAN-CANCER TREATMENT RESPONSE BIOMARKER FOR IMMUNE CHECK-POINT INHIBITOR THERAPIES

April 2022



OPPORTUNITY OVERVIEW

- Dr Zelenay and the team at the Cancer Research UK Manchester Institute, University of Manchester have shown a critical role of COX-2-dependent inflammation in initiating a cancer promoting inflammatory response
- A novel biomarker – COX-2 inflammatory signature (COX-IS) has been developed, integrating both COX-2-associated pro-tumourigenic and anti-tumourigenic inflammatory factors in a multi-gene expression ratio to predict both patient survival and response to immunotherapy in multiple malignancies
- The COX-IS is widely prognostic even when adjusted for age, gender, tumor stage and other disease-specific features
- Strong proof of concept data on overall patient survival predictions across various malignancies, and on treatment outcome predictions for both PD-1/PD-L1 or CTLA-4 blockade therapy across multiple patient cohorts in several cancer types
- The COX-IS outperforms gene signatures centered on T cell inflammation or IFN-γ-signalling and is predictive even in cancer types in which TMB or PDL1 are not associated with response

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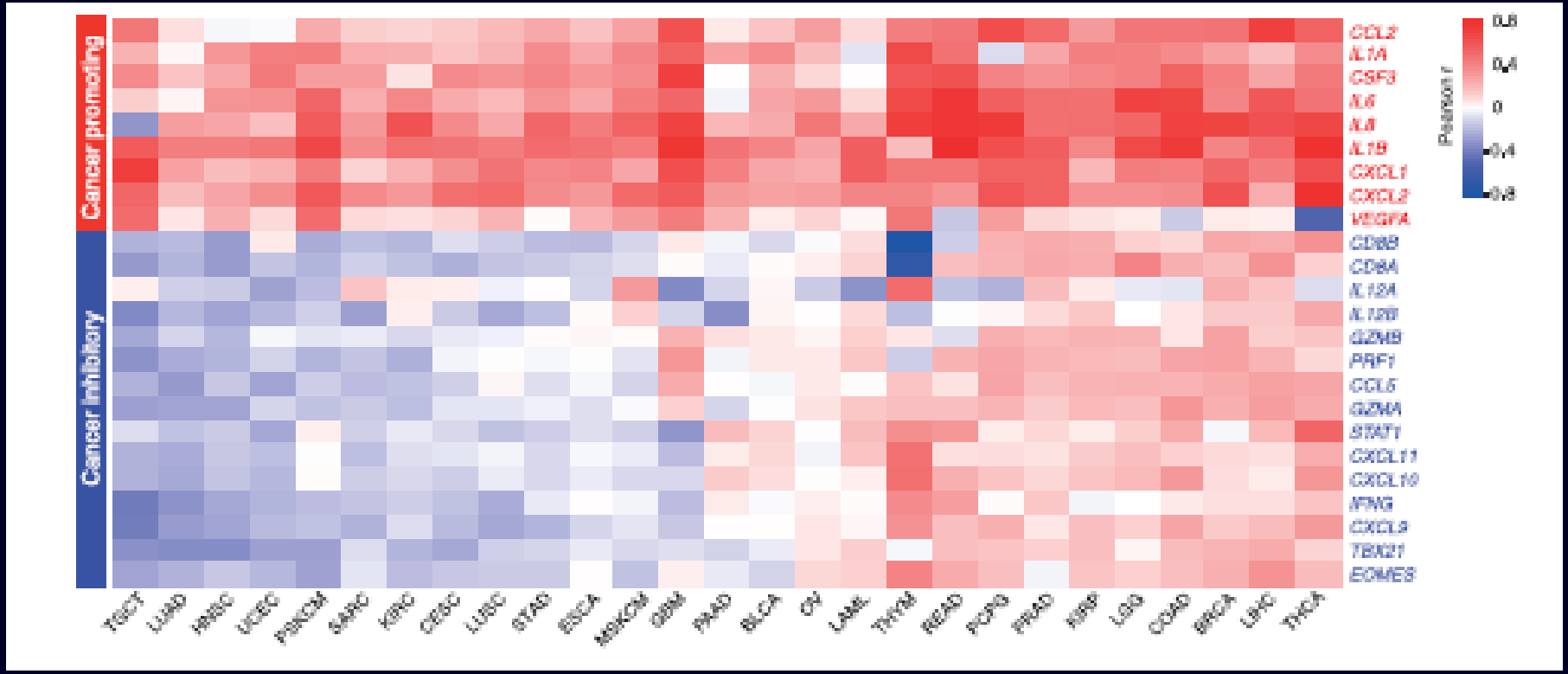
BACKGROUND

- Immune check point inhibitor therapy (ICI) is approved and in active clinical trials for multiple advance cancers treatment
- There is an unmet clinical need for a robust biomarker for determining responsiveness to ICIs

COX2 EXPRESSION IS A HIGHLY DYNAMIC BIOMARKER TRAVERSING CANCER TYPES

COX-2 expression can be used to delineate Cancer-Promoting (CP) from Cancer-Inhibitory (CI) inflammation in many human cancers

*The **positive and negative association of COX-2 with CP and CI factors, respectively, are highly statistically significant** in tumours as shown in the figure below. Here Dr Zeleney's group show the correlation of PTGS2 (codes for COX-2) expression across **different human cancer datasets***

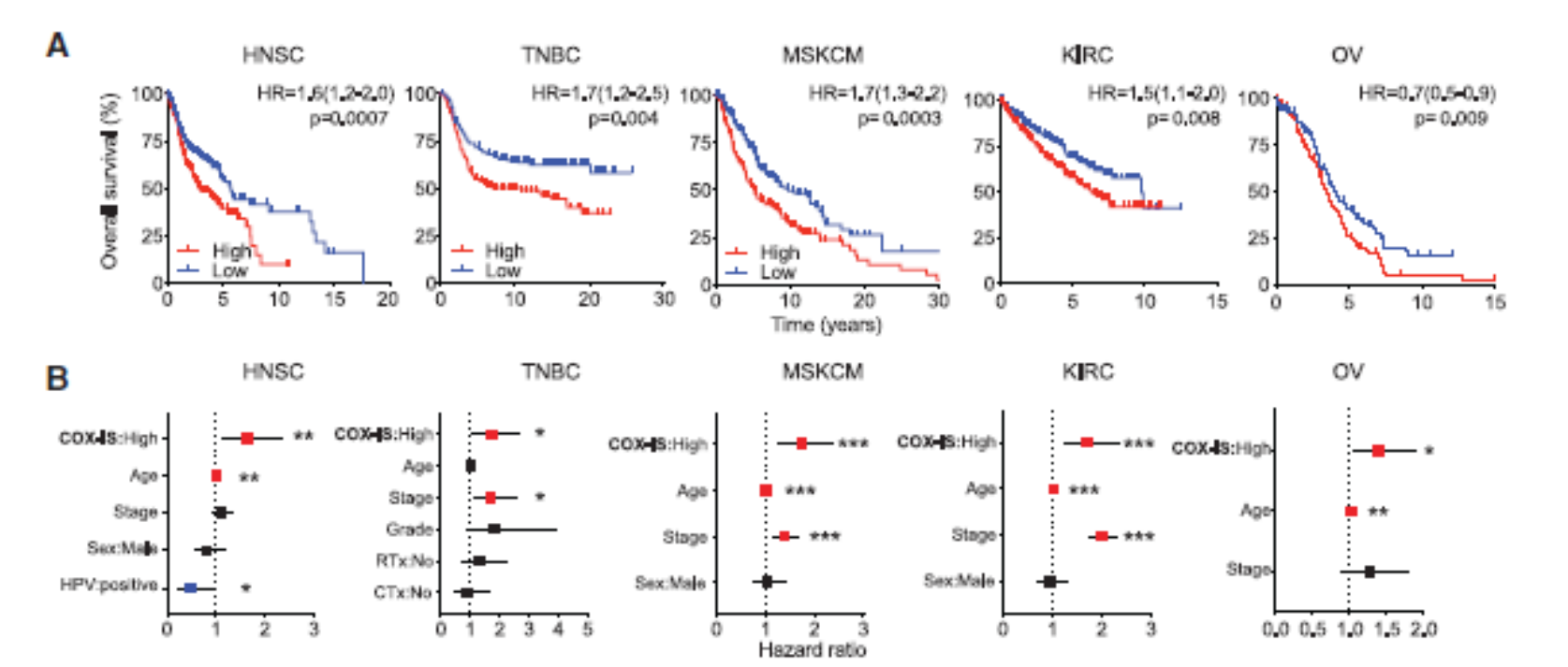


COX-IS CAN BE USED ACROSS MULTIPLE CANCER TYPES, AGE, GENDER, TUMOUR STAGE AND OTHER FEATURES

The COX-IS is an Independent Prognostic Factor useful across a multitude of disease-specific features

Dr Zeleney's group show in figure A below that survival of patients with multiple cancer types can be effectively stratified using COX-IS. ***Patients with higher COX-IS had worse outcomes in all malignancies tested.***

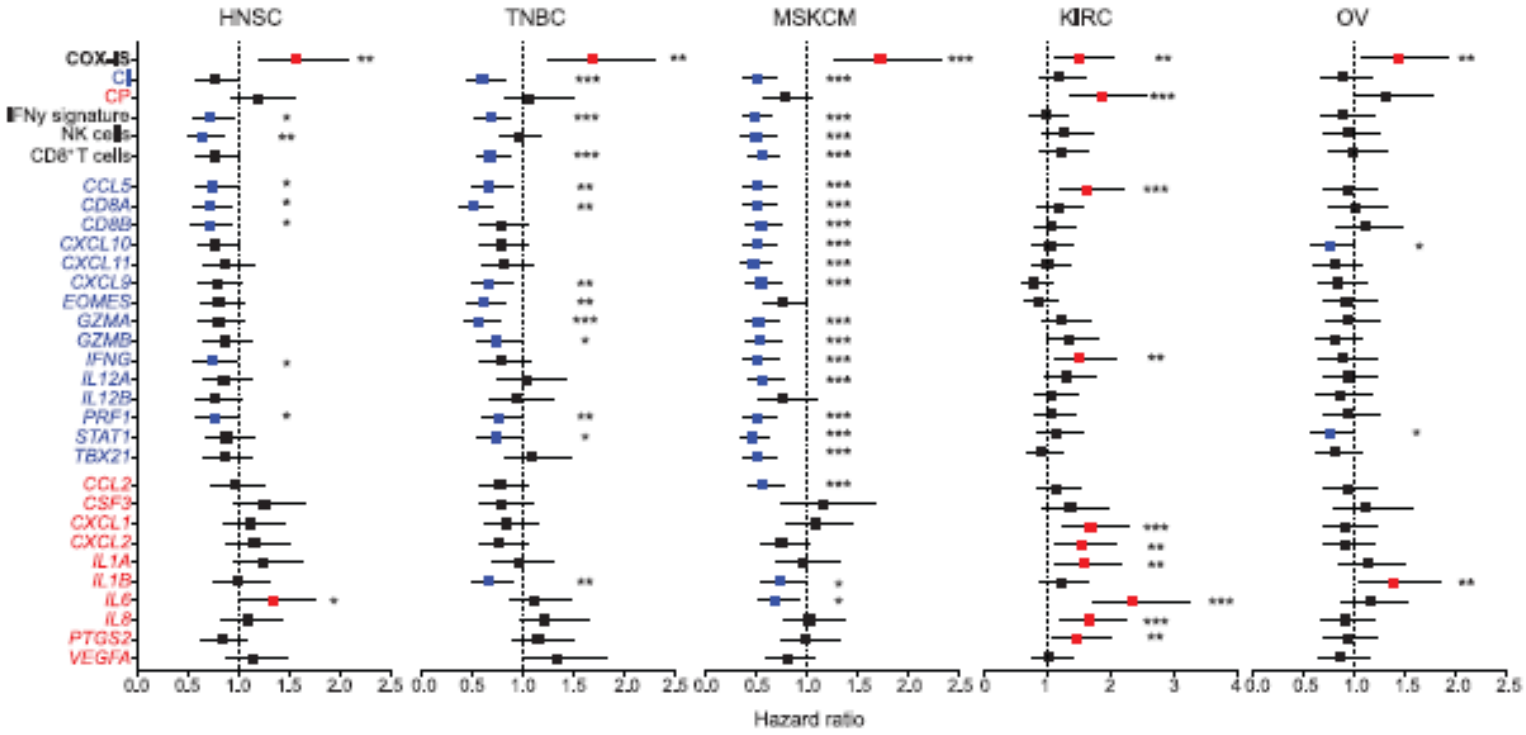
In Figure B, Dr Zeleney's group show a multivariate Cox regression analysis when adjusted for multiple factors including ***age, gender, tumour stage, and other disease-specific features****.*



COX-IS IS A POWERFUL COMBINATION OF MANY COMPONENT CANCER-INHIBITORY AND CANCER-PROMOTING FACTORS

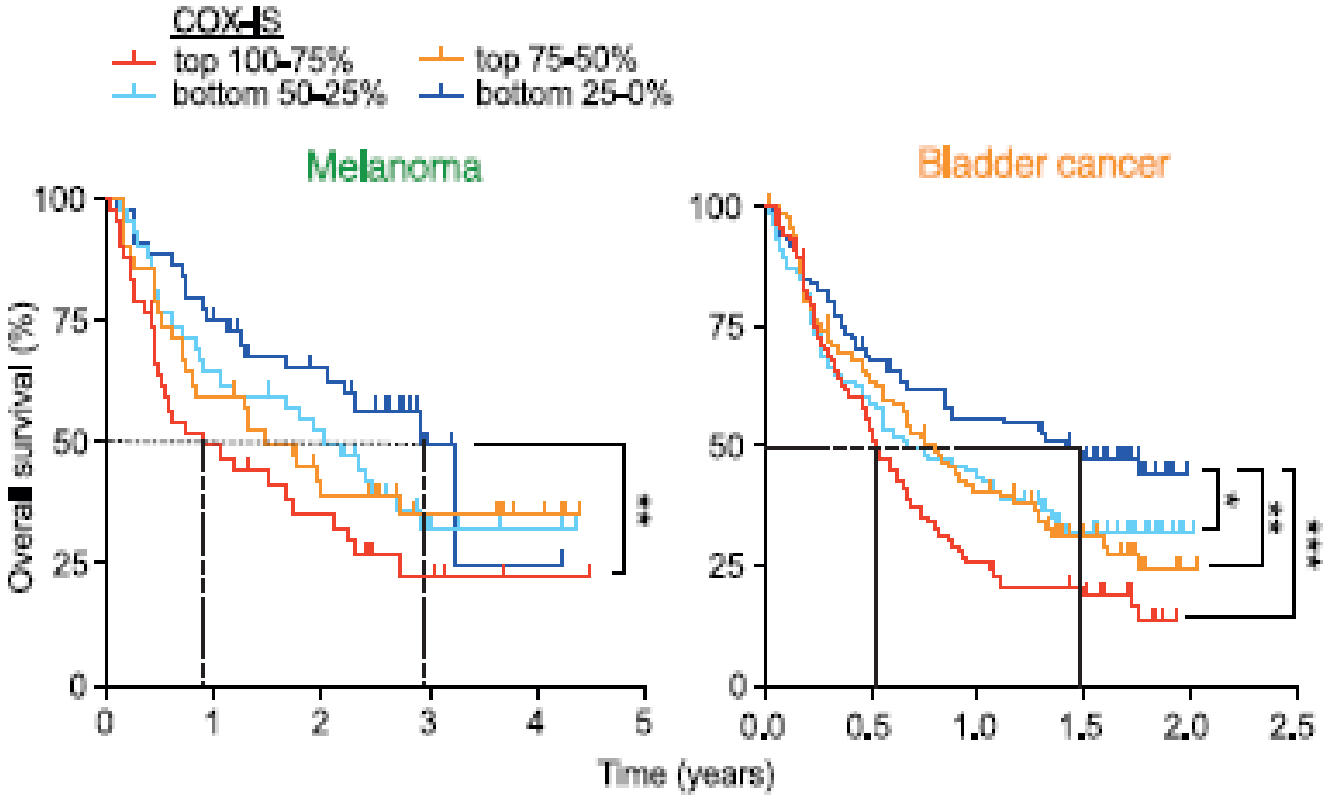
The COX-IS signature relies on the big picture generated by its component parts and outperforms other signatures.

In the figure below, Dr Zeleney's group show the hazard ratio associated with other gene signatures and the individual gene elements of the COX-IS. ***It is the combination of these individual elements that makes COX-IS unique****.*



SURVIVAL CAN BE EFFECTIVELY TRACKED USING COX-IS IN MULTIPLE CANCER TYPES

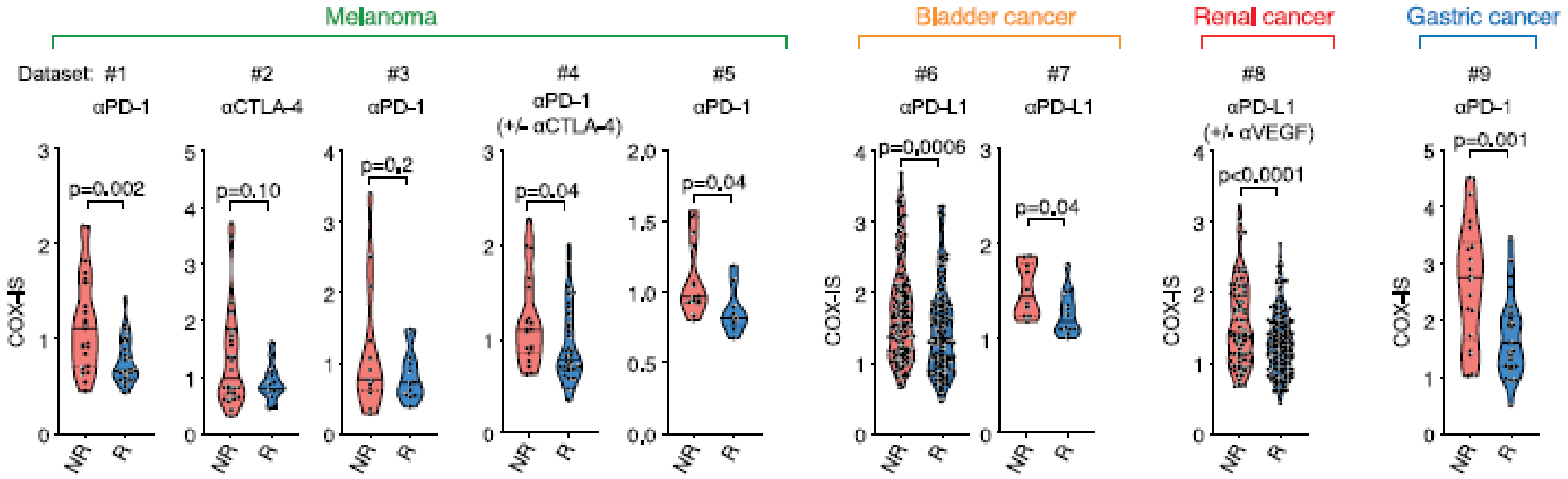
Using the COX-IS signature, patient survival with Melanoma and Bladder cancer patients can be clearly tracked as shown in the figure below.



COX-IS IS A ROBUST BIOMARKER FOR DETERMINING RESPONSIVENESS TO ICIS

The COX-IS signature fulfils an unmet need in predicting the outcome of ICI in patients across multiple cancer types and in multiple ICI drugs/combinations (PD-L1 and CTLA-4).

***COX-IS is lower in patients that benefited from ICI than in those that did not**, regardless of the cancer type or the immune checkpoint drug used. R - Responder and NR - Non-Responder.*



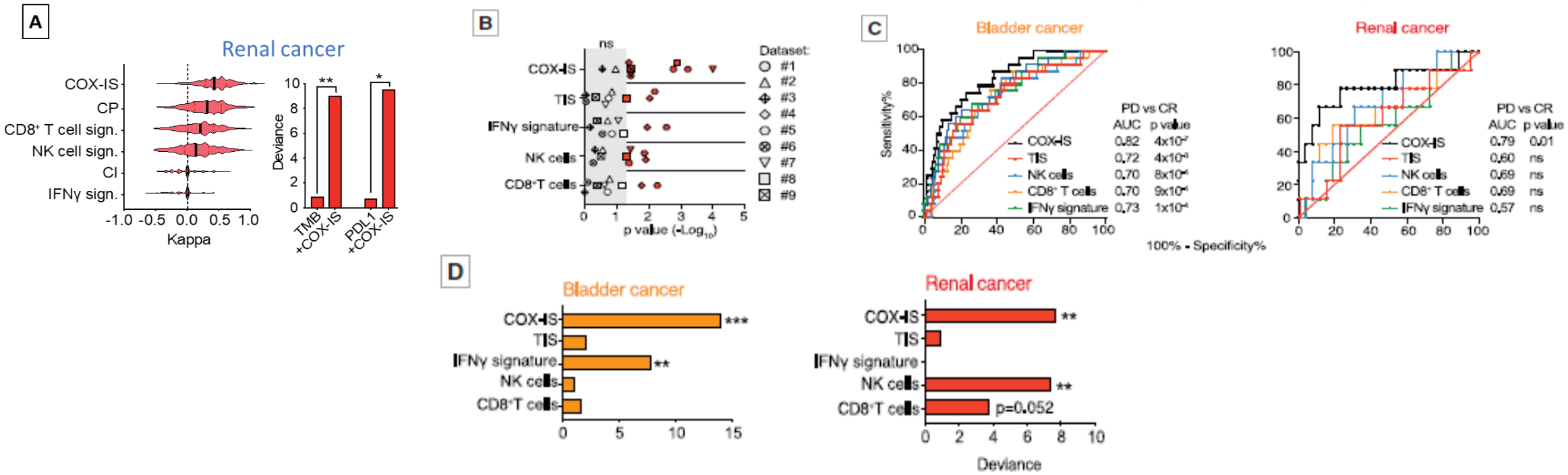
THE COX-IS IS BETTER AT DETERMINING ICI RESPONSIVENESS THAN OTHER SIGNATURES ACROSS CANCER TYPES

The COX-IS is more powerful and reliable at distinguishing responders from non responders than CD8+ T cell, NK cell, or IFN-g signatures or the T cell-inflamed signature across cohorts.

Figure A shows that the COX-IS associates with immune checkpoint blockade outcome irrespectively of treatment and cancer type even in cancer types where ***TMB or PDL1 fail to do so***

Figure B shows COX-IS ***superior performance*** *against other signatures in multiple cohorts and Figure C shows a deeper breakdown of COX-IS sensitivity against the other signatures in two of the largest cohorts available for analysis.*

Figure D shows that ***COX-IS is superior to TIS, IFN-g , or CD8+ T cell signatures*** *in both bladder cancer and RCC in predicting responsiveness to ICB in Different Tumour Types*



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- **The COX-2 inflammatory signature technology is available for direct licensing or co-development**
- **The COX-IS IP is protected by a patent application WO2019243567A1**

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