Using a Knowledgebase of Clinical Assertions to Identify Potential Therapy Targets for Investigation in Underserved Cancers

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Introduction

Despite the recognized oncogenicity of certain gene alterations, many lack established therapeutic options. We leveraged the Velsera Knowledgebase (KB), which covers available associations of clinical relevance in cancer to 1250+ genes including numerous biomarker-disease-therapy associations, to identify potential molecular targets in cancer types with a paucity of therapeutic options.

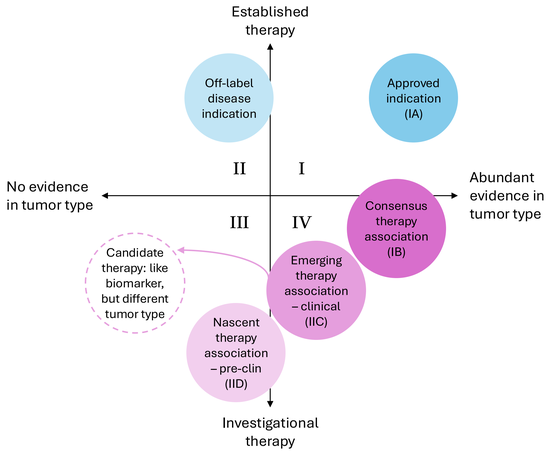


Figure 1. While approved and practice-guideline recommended therapies (quadrant I, blue circle) are obvious targets for investigation in other indications, emerging biomarkers with early evidence of predictive value from human oncology studies (quadrant IV) are difficult to catalog and search comprehensively—yet may offer promise in tumor types in which they have not yet been studied. Evidence that can support classification of genomic variants at AMP/ASCO/CAP Tier IIC includes emerging consensus therapy associations from multiple published studies. These are lesser-known than Tier IB therapy associations and may represent "occult" opportunities for drug repositioning in other tumor type contexts.

Methods

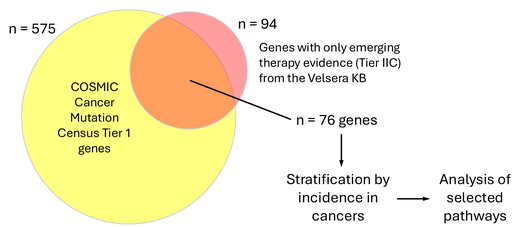


Figure 2. Tier I cancer driver genes (n=575; yellow circle) from the Catalog of Somatic Mutations in Cancer (COSMIC) Cancer Mutation Census (CMC) dataset* were intersected with 94 genes in the Velsera KB as of March 2024 (pink circle) for which alterations are predictive of response to therapies in an investigational setting in one or more solid tumor types, but that lack therapy associations from practice guideline recommendations or drug approvals. This yielded 76 cancer genes, which were further assessed for incidence across tumor types in cBioportal** (frequently altered genes shown in Table 1). Selected commonly altered genes, along with other genes implicated in the same molecular pathways, were analyzed to identify evidence from the Velsera KB that alterations in the genes a) predict response to therapy or b) serve as inclusion criteria for enrolling clinical trials (Tables 2 and 3).

Results

Table 1. Twenty-six genes frequently altered in solid tumors and the classes of therapy that such alterations predict response to, based on AMP/ASCO/CAP IIC evidence from the published literature, according to Velsera's KB. Of the 76 genes with such evidence that are COSMIC CMC Tier I genes, these 24 are present at an incidence of ≥10% in one or more solid tumor types.

Gene	Tumor suppressor or oncogene?	Drug classes that may offer benefit in context of alteration in Gene, IIC evidence
CDKN2A	Tumor suppressor	MEK inhibitor
ARID1A	Tumor suppressor	DNA repair inhibitor, Immunotherapy, mTOR inhibitor + aromatase inhibitor
SMAD4	Tumor suppressor	Tyrosine kinase inhibitor
FAT1	Tumor suppressor	Cyclin-dependent kinase inhibitor
APC	Tumor suppressor	VEGF inhibitor
BAP1	Tumor suppressor	DNA repair inhibitor, Immunotherapy
STK11	Tumor suppressor	mTOR inhibitor
ATRX	Tumor suppressor	DNA repair inhibitor, Immunotherapy
SETD2	Tumor suppressor	DNA repair inhibitor, Immunotherapy
PBRM1	Tumor suppressor	Immunotherapy
PIK3R1	Tumor suppressor	mTOR inhibitor
NF2	Tumor suppressor	FAK inhibitor
SPOP	Tumor suppressor	Hormone inhibitor
NOTCH1	Tumor suppressor/ oncogene	Notch and gamma-secretase inhibitor
MYC	Oncogene	VEGF inhibitor
MDM2	Oncogene	Selective MDM2 inhibitor
CDK4	Oncogene	Topoisomerase inhibitor
CCNE1	Oncogene	Checkpoint kinase inhibitor, DNA repair inhibitor, topoisomerase inhibitor
CTNNB1	Oncogene	BRAF inhibitor mTOR inhibitor +/- hormone inhibitor
FGFR1	Oncogene	VEGFR and FGFR inhibitors
CCND3	Oncogene	Topoisomerase inhibitor
GNAS	Oncogene	Immunotherapy +/- HER2 antibody
CCND2	Oncogene	Topoisomerase inhibitor
TFE3	Oncogene	Kinase inhibitor

Tables 2 and 3. Therapy-gene combinations for genes in the Wnt pathway (left) and DNA repair genes (right) that are predictive of response when altered based on AMP/ASCO/CAP IIC evidence from the published literature ("IIC") or that are under investigation in enrolling clinical trials ("T") in the indicated solid tumor types, based on information curated in the Velsera KB. Genes derive from the list of commonly altered genes in Table 1, those with lower incidence of alteration from the list of 76 genes intersecting with CMC Tier I, and in blue, selected additional genes identified from pathway analysis that have literature evidence or clinical trial data from the Velsera KB. Tumor types shown that lack any indication of evidence or trial eligibility are those in which one or more of the listed genes is frequently mutated, suggestive of potential therapeutic value.

Table 2: Wnt pathway

		Tumor type								
Therapy	Gene	Hepatobiliary cancer	Uterine and cervical cancer	Malignant melanoma	Colorectal cancer	Esophagogastric cancer	Bladder cancer	Prostate cancer	Pancreatic cancer	Non-small cell lung cancer	Any solid tumor
Everolimus + Letrozole	*CTNNB1*		IIC								
Temsirolimus	*CTNNB1*		IIC								
Bevacizumab	*APC*				IIC						
Tegavivint	*CTNNB1*										T
Pembrolizumab + Sirexatamab	*CTNNB1*		T								
Pembrolizumab + Tegavivint	*CTNNB1*	T									
FOG-001	*CTNNB1*					T				T	
REC-4881	*APC*										T
Tegavivint	*APC*										T
Pembrolizumab + Sirexatamab	*APC*		T								
FOG-001	*APC*					T				T	
Tegavivint	*AXIN2*										T
Pembrolizumab + Sirexatamab	*AXIN2*		T								
Pembrolizumab + Tegavivint	*AXIN1*	T									
REC-4881	*AXIN1*										T
Tegavivint	*RNF43*										T
Pembrolizumab + Sirexatamab	*RNF43*		T								

Table 3: DNA repair

		Tumor type													
Therapy	Gene	Pancreatic cancer	Urinary tract cancer	Kidney cancer	Breast cancer	Biliary cancer	Mesothelioma	GIST	Glioma	Colorectal cancer	Prostate cancer	Pancreatic cancer	Non-small cell lung cancer	Malignant melanoma	Any solid tumor
Olaparib	*SETD2*				IIC										
Olaparib	*FANCD2*	IIC													
Atezolizumab	*FANCD2*		IIC												
Pembrolizumab	*FANCD2*		IIC												
Bevacizumab + Everolimus	*FH*			IIC											
Everolimus + Lenvatinib	*FH*			IIC											
Camonsertib	*SETD2*														T
Durvalumab + Olaparib	*FANCD2*					T									
Olaparib	*FANCD2*					T									
Niraparib	*FANCD2*										T	T			
Olaparib + Pembrolizumab	*FANCD2*													T	
Niraparib + hormone inhib	*FANCD2*										T				
Talazoparib	*FANCD2*														T
Axitinib + Toripalimab	*FH*			T											
Bevacizumab + Erlotinib	*FH*														T

Conclusions

Knowledgebases that aggregate emerging associations from published clinical research and enrolling clinical trials are a rich source of therapeutic targets and agents with potential clinical value in indications not yet studied. The intersection of these data with public, commercially available, and private clinicogenomic datasets can short-circuit preclinical target discovery and identify biomarkers worthy of clinical investigation. Here, we demonstrate that emerging targeted therapy associations in a cancer type from the Velsera Knowledgebase can be used in this fashion to repurpose drugs or identify broader indications worthy of study.

*COSMIC Cancer Mutation Census was downloaded and used according to commercial license terms from https://cancer.sanger.ac.uk/cmc/home
See also 2024 COSMIC publication: https://doi.org/10.1093/nar/gkad986

**cBioportal data were accessed from https://www.cbioportal.org/ considering driver mutations for solid tumors with 100+ samples per cancer type from the following datasets: MSK-IMPACT Clinical Sequencing Cohort (MSK, Nat Med 2017), China Pan-cancer (OrigiMed, Nature 2022), MSK MetTropism (MSK, Cell 2021)

Future Directions

Tumor types with high incidence of alteration in a gene that is an emerging therapeutic target in one or more other tumor types represent candidate indications for investigation. Velsera's comprehensive Knowledgebase can be used to identify which candidate tumor types lack published evidence or are not eligible for existing clinical trials. Such an analysis can be conducted at the level of each specific investigational therapy to reveal therapy-specific gaps in evidence, revealing opportunity for new application of therapies.

Figure 3. A focus on tumor types that that exhibit frequent mutations in a gene but in which an emerging therapy has not yet been tested (column graph) may reveal disease targets worth pursuing. For a given emerging therapy with promise in the context of alterations in a given gene, comparing the full set of tumor types with high incidence of alterations (blue-grey circle) with a) those tumor types with emerging evidence, from the Velsera KB, of benefit of therapies in the context of that altered gene (orange circle) and b) those tumor types under study for investigational therapies in the context of that altered gene in recruiting clinical trials in the Velsera KB (green circle) reveals those tumor types that may not have yet been investigated.

