AVVISO PUBBLICO, PER TITOLI E COLLOQUIO, PER L'ASSUNZIONE A TEMPO DET. N 2 RISORSE NELL'AMBITO DEL PROGETTO CODICE PNC0000001, DAL TITOLO "D3 4 HEALTH, - DIGITAL DRIVEN DIAGNOSTICS, PROGNOSTICS AND THERAPEUTICS FOR SUSTAINABLE HEALTH CARE" P.I. PROF. GENNARO CILIBERTO, CUP B53C22006010001

Domande

TECNICA:

1) Descrivere il ruolo degli organoidi nella medicina di precisione in oncologia

2) Descrivere le condizioni sperimentali che hanno permesso l'isolamento e la crescita di organoidi che derivano da tumori di pazienti (es. head & neck)

3) Descrivere le condizioni sperimentali che hanno permesso l'isolamento e la crescita di organoidi che rappresentano il tumore perché costituiti da tutte le cellule che lo compongono (i.e. cellule tumorali, cellule del microambiente tumorale e matrice extracellulare).

INFORMATICA:

1. Cosa rappresenta un "heatmap" nell'analisi dei dati di espressione genica?

2. Dare una definizione di algoritmo.

3. Cos'è il valore p (p-value) nell'analisi statistica dei dati di espressione genica?

Istituti Fisioterapici Ospitalieri - ROMA

IN FOCUS

Precision Oncology: 2023 in Review

Yonina R. Murciano-Goroff[1], Sarah P. Suehnholz[2,3], Alexander Drilon[1,4], and Debyani Chakravarty[2,3]

Summary: This article presents a review of recent major advances in precision oncology and the future implications of these advances, specifying the iterative progress achieved from the end of 2022 through 2023. We discuss the different classes of precision oncology drugs and associated biomarkers as well as the improvements in clinical trial design that have enabled the efficient testing of these drugs.

INTRODUCTION

1 The scope of precision oncology continues to expand as drugs with new mechanisms of action enable therapeutic intervention on a wider array of targets in broader, biomarker-selected patient populations. By virtue of the advances in our understanding of specific mutation-based clinical implications and the epistatic relationship between co-occurring mutations, as well as the role that the immune environment plays in therapy selection, the long-standing paradigm of matching a single gene to a single treatment is rapidly evolving.

2 This review, as the second installment in the Precision Oncology Year in Review series (1), uses OncoKB to offer a lens into the advances in precision oncology in 2023. On the basis of OncoKB, as of November 2023, twelve treatments were approved by the FDA for unique biomarker-selected indications, and six biomarker- and indication-specific treatments were listed in the National Comprehensive Cancer Network (NCCN) guidelines in the past year. In addition, compelling clinical evidence for two precision oncology therapies led to their inclusion as level 3 investigational agents in OncoKB (Table 1). Here we discuss the growing array of targetable molecular alterations as well as the proteomic and immunologic biomarkers that are increasingly guiding patient matching to novel classes of medications, including antibody–drug conjugates (ADC) and proteolysis-targeting chimeras (PROTAC)/protein degraders, and how the distinct biology of individual mutant alleles has contributed to drug development efforts.

3

CHIPPING AWAY AT THE UNDRUGGABLE

Over the past couple of years, novel approaches to drug design have resulted in new precision oncology therapies that are proving to be successful in addressing an increasing number of previously undruggable targets in the cli Epitomizing the cumulative results of these developmen our current emerging ability to target *KRAS*-mutant can initiated with the success of selective $KRAS^{G12C}$ inhibitors

The $KRAS^{G12C}$ inhibitors sotorasib and adagrasib, both which trap $KRAS^{G12C}$ in its inactive GDP-bound state, p ously received accelerated approval for $KRAS^{G12C}$-mutant n small cell lung cancer (NSCLC). These inhibitors are now li in the NCCN guidelines additional $KRAS^{G12C}$-mutant hist gies, including for pancreatic and colorectal cancers (the la indication's approval is in combination with either anti-E monoclonal antibody inhibitors cetuximab or panitumun Another more potent $KRAS^{G12C}$ inhibitor of GDP-bound KI divarasib, was shown to achieve an initial overall respo rate (ORR) of 54% and progression-free survival (PFS) of months in patients with NSCLC treated on a phase I trial (2

$KRAS^{G12C}$ has a slightly increased affinity for GTP ve GDP, and this past year, the field pivoted to develop *KRAS* inhibitors that trap the oncoprotein in its activated or so-c "on" form. For example, FMC-376 is a covalent inhibitor of t the activated and inactivated forms of $KRAS^{G12C}$, and R 6291, employs the formation of a so-called "tricomplex" betw KRAS, cyclophilin A, and the drug to inhibit $KRAS^{G12C}$ i activated state. There has also been a pronounced empl on combining $KRAS^{G12C}$ inhibitors with other agents this These combination strategies include supplementing *KRAS* inhibitor treatment with drugs that target emerging biomar such as integrin beta 4 (3) as well as with immunotherapy, ch otherapy or other precision oncology drugs including those target known resistance alterations arising in the receptor ty ine kinase (RTK) or mitogen activated protein kinase (MA pathways. Preliminary data on the combination of the *KRAS* "off" inhibitor LY3537982 with pembrolizumab showed ORR of 78% in NSCLC with no prior G12C inhibitor expo and 25% after prior G12C inhibitor exposure (4).

Non-G12C KRAS alleles, including both mutant-sele and pan-KRAS inhibitors, are also being explored. For ex ple, $KRAS^{G12D}$, the most common KRAS allele pan-canc now potentially targetable by agents including RMC-98 tricomplex inhibitor; MRTX1133, a noncovalent inhib and ASP3082, a protein degrader. Multiallele KRAS inhib such as RMC-6236 achieved clinical responses in G12D- G12V-mutant cancers in a phase I trial (5). Lastly, pan-K inhibitors that avoid inadvertant HRAS and NRAS activa by KRAS wild-type cells are in preclinical development (6

Other targets previously considered undruggable includ YAP transcription coactivator, the phosphorylation and su

[1]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York. [2]Marie-Josée and Henry R. Kravis Center for Molecular Oncology, Memorial Sloan Kettering Cancer Center, New York, New York. [3]Department of Pathology and Laboratory Medicine, Memorial Sloan Kettering Cancer Center, New York, New York. [4]Weill Cornell Medical College, New York, New York.

Corresponding Authors: Debyani Chakravarty, Memorial Sloan Kettering Cancer Center, 323 East 61st Street, Room 615, New York, NY 10065. E-mail: chakravd@mskcc.org; and Alexander Drilon, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065. E-mail: drilona@mskcc.org

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