Domanda estratta n. 2

Quesiti prova colloquio per l'avviso pubblico, per titoli e colloquio, per l'assunzione a tempo determinato di n. 1 posto di ricercatore sanitario, categoria ds, per laureati in medicina e chirurgia - progetto PNRR, codice PE00000019, finanziato dall'Unione Europea – next generation eu, dal titolo "Health extended alliance for innovative therapies, advanced lab-research, and integrated approaches of precision

1. Il ruolo degli oncosoppressori e i principali tumor-suppressor gene

2. Epistasi: definizione, applicazione in oncogenomica, e principali esempi.

Istituti Fisioterapici Ospitalieri - ROMA

Domanda estratta n. 1

Quesiti prova colloquio per l'avviso pubblico, per titoli e colloquio, per l'assunzione a tempo determinato di n. 1 posto di ricercatore sanitario, categoria ds, per laureati in medicina e chirurgia - progetto PNRR, codice PE00000019, finanziato dall'Unione Europea – next generation eu, dal titolo "Health extended alliance for innovative therapies, advanced lab-research, and integrated approaches of precision

1. Che cosa è un Data Base.
2. Citi e illustri i principali applicativi/software da utilizzare in ambito di ricerca scientifica.

Istituti Fisioterapici Ospitalieri - ROMA

Comutations and KRAS^{G12C} Inhibitor Efficacy in Advanced NSCLC

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ABSTRACT Molecular modifiers of KRAS^{G12C} inhibitor (KRAS^{G12Ci}) efficacy in advanced *KRAS*^{G12C}-mutant NSCLC are poorly defined. In a large unbiased clinicogenomic analysis of 424 patients with non–small cell lung cancer (NSCLC), we identified and validated coalterations in *KEAP1*, *SMARCA4*, and *CDKN2A* as major independent determinants of inferior clinical outcomes with KRAS^{G12Ci} monotherapy. Collectively, comutations in these three tumor suppressor genes segregated patients into distinct prognostic subgroups and captured ~50% of those with early disease progression (progression-free survival ≤3 months) with KRAS^{G12Ci}. Pathway-level integration of less prevalent coalterations in functionally related genes nominated PI3K/AKT/MTOR pathway and additional baseline *RAS* gene alterations, including amplifications, as candidate drivers of inferior outcomes with KRAS^{G12Ci}, and revealed a possible association between defective DNA damage response/repair and improved KRAS^{G12Ci} efficacy. Our findings propose a framework for patient stratification and clinical outcome prediction in *KRAS*^{G12C}-mutant NSCLC that can inform rational selection and appropriate tailoring of emerging combination therapies.

SIGNIFICANCE: In this work, we identify co-occurring genomic alterations in *KEAP1*, *SMARCA4*, and *CDKN2A* as independent determinants of poor clinical outcomes with KRAS^{G12Ci} monotherapy in advanced NSCLC, and we propose a framework for patient stratification and treatment personalization based on the comutational status of individual tumors.

See related commentary by Heng et al., p. 1513.

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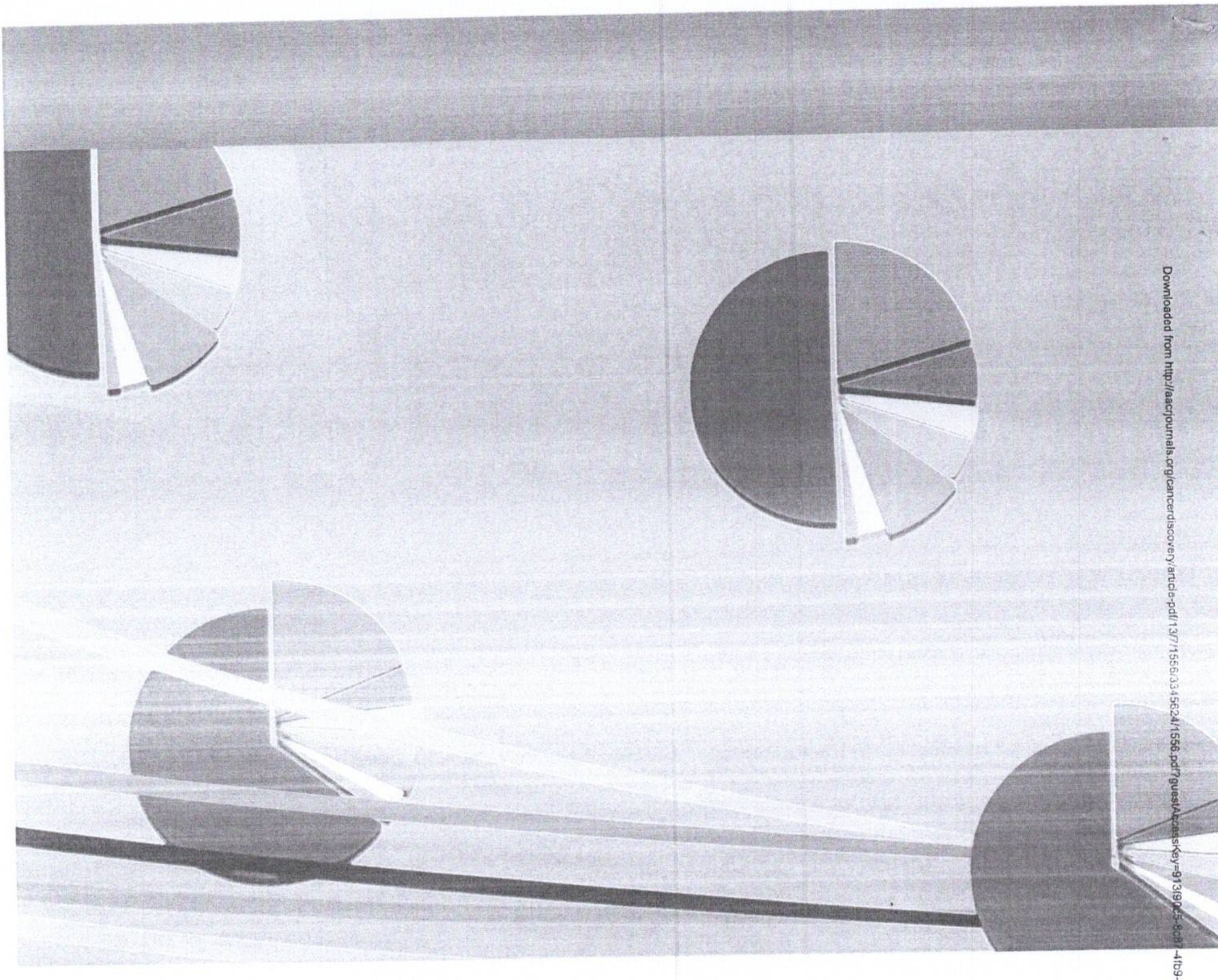

INTRODUCTION

Activating mutations in the *KRAS* proto-oncogene are detected in 25% to 30% of nonsquamous non–small cell lung cancer (NSCLC) and most frequently (~42%) involve a glycine to cysteine substitution at residue 12 (G12C) as a result of a smoking-related G>T transversion (1). Replacement of glycine in codon 12 of KRAS is thought to sterically hinder insertion of the arginine finger (R-finger) of canonical GTPase activating proteins (GAP; such as neurofibromin and p120RasGAP) into the GTPase active site and impairs GAP-stimulated GTP hydrolysis (2), thus shifting the KRAS nucleotide cycling equilibrium toward the active, GTP-bound state. For over 30 years since its initial discovery, KRAS remained an elusive therapeutic target due to (i) picomolar binding affinity for its guanine nucleotide substrates coupled with a high intracellular concentration of GTP, thus precluding the development of competitive inhibitors; (ii) a featureless protein surface devoid of deep pockets suitable for docking of small-molecule inhibitors; (iii) on-target toxicity from wild-type KRAS inhibition or concurrent targeting of the downstream effector RAF/

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MEK/ERK and PI3K/AKT/MTOR pathways; (iv) paradoxical increase in RAS signaling with downstream pathway inhibitors due to release of negative feedback; and (v) redundant prenylation pathways that control KRAS plasma membrane localization (3). The groundbreaking identification of compounds and subsequent development of covalent allosteric inhibitors that bind irreversibly to cysteine 12 and occupy a cryptic induced pocket in the switch II region of GDP-bound KRAS, trapping the oncoprotein in its inactive conformation, has enabled effective inhibition of $KRAS^{G12C}$ (4, 5). Sotorasib (formerly AMG510), the first-in-class $KRAS^{G12C}$ inhibitor ($KRAS^{G12Ci}$), and adagrasib (formerly MRTX849) both yielded robust single-agent clinical activity in previously treated patients with advanced *KRAS*^{G12C}-mutant NSCLC, producing objective response rates (ORR) of 37% to 43% in single-arm registrational phase II studies (6, 7). Based on these results, both sotorasib and adagrasib received FDA accelerated approval for previously treated patients with advanced *KRAS*^{G12C}-mutant NSCLC; furthermore, sotorasib improved progression-free survival (PFS) and ORR compared with docetaxel in the randomized phase III CodeBreaK 200 trial (8). Several additional $KRAS^{G12C}$ inhibitors are undergoing clinical development, with initial reports indicating comparable single-agent activity (9–12).

1 Despite promising ORR, $KRAS^{G12Ci}$ produce a median PFS of approximately 6 to 7 months (6, 7), which is inferior to what has been reported for targeted therapies in other oncogene-addicted NSCLC subsets (e.g., *EGFR* mutations or *ALK* rearrangements; refs. 13, 14). For individual patients, clinical outcomes with $KRAS^{G12Ci}$ vary widely from long-term durable responses and prolonged survival—with a 2-year overall survival (OS) rate of 32.5% reported in CodeBreaK 100—to early disease progression seen in ~5% to 16% of treated patients (6, 7, 15). *De novo* as well as adaptive and acquired resistance collectively curtail the efficacy of $KRAS^{G12Ci}$ monotherapy (7, 15–20), and support the need for improved patient selection for sotorasib or adagrasib monotherapy and for combination regimens directed at treatment intensification. However, molecular or clinical determinants of distinct clinical outcomes with $KRAS^{G12Ci}$ are hitherto poorly defined, and validated markers for patient stratification prior to treatment initiation are lacking. Co-occurring genomic alterations in key tumor suppressor genes underpin the molecular diversity of *KRAS*-mutant NSCLC and impact both tumor cell–intrinsic and nontumor cell–autonomous cancer hallmarks, including shaping its immune contexture (21, 22). Critically, comutations can impact responses to standard-of-care systemic therapies, including both chemotherapy and immunotherapy (22–26). Here, we systematically dissected the impact of genomic and clinical features on outcomes with $KRAS^{G12Ci}$ in the largest cohort to date of NSCLC patients treated with sotorasib or adagrasib, encompassing 424 patients from 21 centers in the United States and Europe. We demonstrate that prevalent coalterations in *KEAP1*, *SMARCA4*, and *CDKN2A* are associated with inferior clinical outcomes with $KRAS^{G12Ci}$ therapy and collectively define a subgroup of patients with poor prognosis. In addition, we identify less prevalent candidate genomic modifiers of $KRAS^{G12Ci}$ efficacy and propose a framework for patient stratification with implications for treatment selection and clinical trial development for *KRAS*^{G12C}-mutant NSCLC.

RESULTS

Clinical Outcomes with $KRAS^{G12Ci}$ Monotherapy in Advanced NSCLC

2 In order to comprehensively interrogate the impact of baseline clinicogenomic parameters on clinical outcomes with $KRAS^{G12Ci}$, we assembled the largest cohort to date of patients with *KRAS*^{G12C}-mutant NSCLC who were treated with sotorasib or adagrasib, encompassing 424 unique evaluable patients across 21 centers in the United States and Europe (Supplementary Table S1). The study cohort was established by merging two independently collected retrospective cohorts [cohort A ($N = 330$) and cohort B ($N = 94$)], which were also analyzed separately to provide additional validation of key findings (Supplementary Tables S2 and S3; see Methods for detailed study eligibility criteria). In the overall cohort, the median age was 68 years, patients were predominantly current or former smokers (96.9%), and most patients had Eastern Cooperative Oncology Group performance status (ECOG PS) 0 to 1 (82.1%). Adenocarcinoma was the most common histology (92.7%). All patients had metastatic disease at the start of $KRAS^{G12Ci}$ therapy, and 35.2% had a history of brain metastases (26.2% previously treated, 9.0% untreated). The majority of patients received treatment with sotorasib (83.3%). Most patients received prior treatment with PD-1/PD-L1 inhibitors and platinum-based chemotherapy (75.9%). This cohort was overall representative of the general population of patients with *KRAS*^{G12C}-mutant NSCLC (6, 7). Most patients had genomic profiling performed on tumor tissue (62.3%), 18.2% had genomic profiling results from the liquid biopsy, and 13.7% had both tumor and liquid biopsy profiling; 5.8% of patients had confirmed *KRAS*^{G12C} status from analysis of tumor DNA but did not undergo next-generation sequencing–based profiling. Patient characteristics for the overall study cohort are summarized in Supplementary Table S1. In the overall cohort, ORR was 34.0% [95% confidence interval (CI), 29.4–38.8], median PFS was 5.2 months (95% CI, 4.7–5.6), and median OS was 10.7 months (95% CI, 8.8–12.6; Fig. 1A). The estimated 12-month PFS and OS rates were 22.2% and 46.3%, respectively, whereas the estimated 24-month PFS and OS rates were 6.4% and 23.3%, respectively. We observed similar results when analyzing the individual cohorts separately (Supplementary Fig. S1A and S1B). ECOG PS of 1 or 2 was associated with shorter PFS and OS compared with PS 0, and patients with a history of brain metastases had worse PFS and OS with $KRAS^{G12Ci}$ therapy compared with those without prior history of brain metastasis (Fig. 1B). No difference in PFS and OS was observed depending on the $KRAS^{G12Ci}$ used (Fig. 1B). When the analysis was limited to previously treated patients with ECOG PS 0 to 1 and either absent or treated and stable brain metastases at start of $KRAS^{G12Ci}$ therapy (comparable with the patient population enrolled in the registrational CodeBreaK 100 and KRYSTAL-1 clinical trials; refs. 6, 7), the ORR was 35.0% (95% CI, 29.1–41.1), the median PFS was 5.5 months (95% CI, 4.9–6.0) and the median OS was 11.4 months (95% CI, 8.8–14.1; Supplementary Fig. S2A). Patients with untreated brain metastases had similar survival compared with those with previously treated brain metastases [PFS: 5.0 vs. 4.3 months, log-rank $P = 0.964$, multivariable (MV) hazard ratio (HR) 0.95 (95% CI, 0.82–1.44); OS: 8.8 vs.

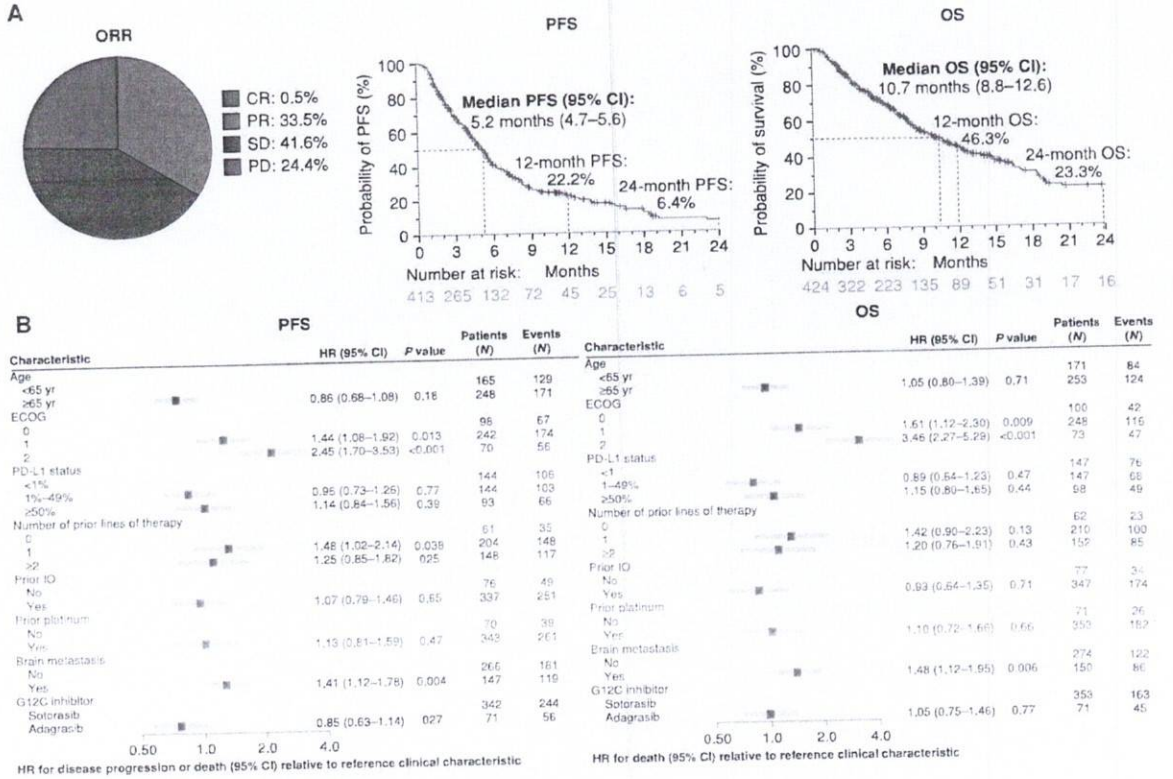

Figure 1. Clinical outcomes with KRAS^{G12C} monotherapy in the overall study cohort. **A,** Objective response rate, PFS, and OS upon treatment with KRAS^{G12Ci} in advanced *KRAS*^{G12C}-mutant NSCLC. **B,** Forest plot representation of clinical characteristics and their impact on PFS and OS. CI, confidence interval; CR, complete response; HR, hazard ratio; IO, immunotherapy; PD, progressive disease; PR, partial response; SD, stable disease.

7.8 months, log-rank $P = 0.741$, MV HR 1.13 (95% CI, 0.68–1.88); Supplementary Fig. S2B]. Tumor cell PD-L1 expression and exposure to immune-checkpoint inhibitors in prior line(s) of therapy were not associated with PFS or OS (Fig. 1B; Supplementary Fig. S2C and S2D).

Coalterations in *KEAP1*, *SMARCA4*, and *CDKN2A* Are Associated with Early Disease Progression and Poor Clinical Outcomes with KRAS^{G12Ci}

To dissect the impact of the tumor comutational landscape on clinical outcomes with KRAS^{G12Ci}, we first classified patients into subgroups with durable clinical benefit (PFS ≥6 months; $N = 131$) or early progression (PFS ≤3 months; $N = 124$; total $N = 255$; ref. 18). Patients censored with less than 3 months of follow-up were excluded from this analysis. We then performed an unbiased enrichment analysis of the most prevalent coalterations (detected in at least 5% of patients) in the overall study cohort (see Methods for additional details). We found that comutations in three tumor suppressor genes were significantly enriched in the early progression subgroup: *KEAP1* [Fisher exact test $P < 0.001$, false discovery rate (FDR) q = 0.004], *SMARCA4* (Fisher exact test $P = 0.001$, FDR q = 0.010), and *CDKN2A* (Fisher exact test $P = 0.006$, FDR q = 0.034; Fig. 2A). Patients bearing *KEAP1* comutated tumors (*KEAP1*^{MUT}) exhibited significantly shorter PFS [2.8 vs. 5.4 months, log-rank $P < 0.001$, MV HR 2.26 (95% CI, 1.60–3.19)] and OS [6.3 vs. 11.1 months, log-rank $P < 0.001$, MV HR 2.03 (95% CI, 1.38–2.99)] compared with those harboring *KEAP1* wild-type (*KEAP1*^{WT}) NSCLC (Fig. 2B). *SMARCA4* comutations were associated with markedly worse PFS and OS compared with *SMARCA4* wild-type [*SMARCA4*^{MUT} vs. *SMARCA4*^{WT} PFS: 1.6 vs. 5.4 months, log-rank $P < 0.001$, MV HR 3.04 (95% CI, 1.80–5.15); OS: 4.9 vs. 11.8 months, log-rank $P < 0.001$, MV HR 3.07 (95% CI, 1.69–5.60); Fig. 2C]. Coalterations in *CDKN2A* were also associated with worse PFS and OS upon treatment with KRAS^{G12Ci} compared with *CDKN2A* wild-type [*CDKN2A*^{MUT} vs. *CDKN2A*^{WT} PFS: 3.4 vs. 5.3 months, log-rank $P < 0.001$, MV HR 1.98 (95% CI, 1.32–2.97); OS: 6.4 vs. 10.7 months, log-rank $P = 0.009$, MV HR 1.66 (95% CI, 1.03–2.68); Fig. 2D]. Similar findings were observed when cohorts A and B were analyzed separately (Supplementary Fig. S3A–S3C) and when limiting the analysis only to patients who received prior immune-checkpoint inhibitor therapy (Supplementary Fig. S4A–S4C). *KEAP1* comutations were associated with numerically lower ORR compared with *KEAP1*^{WT}, whereas there was no significant difference in ORR between patients with *SMARCA4*^{MUT} versus *SMARCA4*^{WT} and *CDKN2A*^{MUT} versus *CDKN2A*^{WT} NSCLC (Fig. 2B–D).