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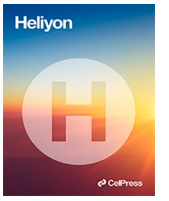

Review article

Unconventional strategy could be the future: From target to KRAS broad range treatment

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A B S T R A C T

The RAS gene family comprises genes that regulate cell growth and differentiation. KRAS, a member of this family, is often mutated in different cancers, resulting in uncontrolled cell growth and tumor development. Recent clinical trial results on KRAS inhibition in NSCLC have defined the presence of a significant proportion of patients resistant to direct G12C inhibition. The presence of co-mutations and the occurrence of secondary resistance phenomena observed in preclinical and clinical settings partly justify these poor results. In addition, all other non-G12C mutations currently remain without specific strategies. Evidence of interactions between KRAS signaling and the TME suggests potential *in vitro* efficacy of immune checkpoint inhibitors. In this short paper, we have reviewed the most relevant data from recent conferences, with a focus on KRAS inhibitors resistance mechanisms and interactions with the peri-tumor immune system.

Commentary.

1. Introduction

Treatment with immune checkpoint inhibitors (ICIs), both as single-agents or in combination with chemotherapy (CT), is the new backbone of systemic therapy for patients with treatment-naïve metastatic non-small cell lung cancer (NSCLC). However the overall survival for advanced NSCLC is approximatively 20 %, as efficacy of treatments relates to several clinical and bio-molecular factors, including gender, race, tumor burden, *EGFR* and *ALK* alterations, PD-L1 expression, as well as the cellular composition of the tumor microenvironment (TME) [1]. , .

RAS proteins are the intramembrane hub involved in connecting the receptor tyrosine kinases (RTKs) signaling to several downstream effectors involved in proliferation, immortalization, and motility [2] (Fig. 1).RAS oncogenic mutations are the main contributors in the development of several human cancers as per pancreatic adenocarcinoma, colon rectal cancers and NSCLC. KRAS mutations occur in approximately 15–25 % of patients affected with lung adenocarcinoma (LUAD) [3], with G12C and G12V substitutions on the winner's spot [4]. The development of G12C inhibitors (G12Cis), some of which (i.e., sotorasib and adagrasib) have been recently introduced in the clinical practice of advanced LUAD, have radically modified the historical concept of RAS undruggability. Although G12Cis have shown promising antitumor activity in advanced NSCLC progression, free survival (PFS) rate of both G12Cis is still disappointing so far [5,6].

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1.1. KRAS inhibitors history

In 2013, Ostrem and colleagues made progress by developing compounds that irreversibly bind to the cysteine residue of the KRASG12C mutation [7]. The most potent compound, compound 12, was subsequently optimized into ARS-853, which demonstrated enough pharmacological potency to be considered a drug candidate [8]. In May 2021, AMG510 (sotorasib) became the first FDA-approved therapy, followed shortly by MRTX849 (adagrasib). Although the safety data is reassuring with G12Cis, median overall survival (mOS; 9.5 months; 95 % confidence interval 8.6–12.0) data from the EAP study-436 recently presented at the ELCC 2023, do not align with expectations based on other targeted therapies [9]. On the other hand, many strategies are being developed for other targets than G12C, such as G12V and G12D inhibitors [10,11], and, pan-target agents [12].KRAS inhibitors mechanisms.

KRAS-mutant disease is ultimately far from being defined as curable, probably due to several resistance mechanisms that arise simultaneously and resulting in treatment failure (Fig. 2). While there are few data on primary resistances [13], increasingly emerging data identified several mechanisms of acquired resistances arising under G12Ci. In particular, *in vitro* studies showed the occurrence of secondary mutations after exposure to G12Cis both on switch–II–pocket site, mutations in *trans* with the KRAS allele and KRAS amplifications. For instance, the Q99L second-site mutation confers adagrasib (but not sotorasib) resistance [14]. In addition, G12Ci exposure in patients with different malignancies, demonstrates a heterogeneous alteration onset consisting in amplification, mutation, or deletion of several genes such as *MET, MYC, BRAF, NRAS, PTEN.* A variable rate of patients from 16 to 23 % according to literature experienced secondary KRAS mutations on canonical codons or in very rare sites (i.e., R68S, H95D/Q/R, Y96C) [13,15]. Mechanisms of acquired resistance to treatment that have been identified also include resumed proliferation via RAS-MAPK signaling, and recently Negrao and colleagues described KEAP1, SMARCA4, and CDKN2A as main drivers of resistance to G12C inhibitors [16]. In NSCLC, quiescent cells can acquire the ability to induce KRAS(G12C) in the active state, via epidermal growth factor receptor (EGFR) and Aurora kinase (AURKA) signaling, and sequentially mediate G12Cis resistance [17]. Potentially every RTKs could be involved in RAS-MAPK pathway activation as ERBB2 in the epithelial type [18]. The resistance mechanisms to novel KRAS inhibitors are complex. Evidence shows that reprogramming of proteostasis via IRE1α is a focal point where numerous resistance mechanisms converge in response to KRAS-MAPK inhibition [19]. Finally, another described adaptive strategy of resistance is the malignant cell's phenotype transition. The epithelial-to-mesenchymal transition (EMT) was described at the beginning in NSCLC cell lines with EGFR expression, conferring resistance to first-generation tyrosine kinase inhibitors (TKIs) [20]. Some KRAS-mutant cell lines have been found to develop drug resistance after undergoing EMT, which can be triggered by the activation of TGF-β- or FGFR-driven pathways [18,21]. Given this background, several strategies of vertical (e.g., inhibitors of SHP2, SOS1 and RTK EGFR or ERBB2/3) or horizontal (e.g., inhibitors of mTOR, CDK4/6, AURKA and WEE1) combinations with specific KRAS G12C inhibitors are being pre clinically evaluated and are under investigation in early phase clinical trials [22]. However, the identification of responsive tumors for each combination

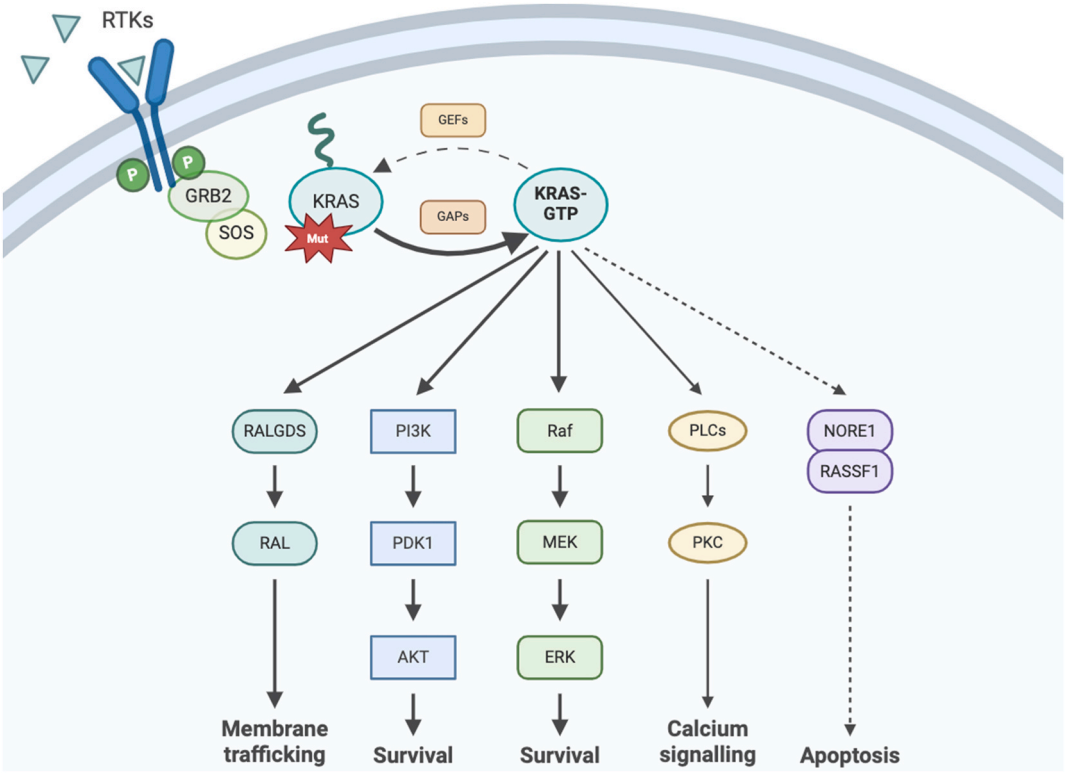

Fig. 1. Schematic representation of RAS mutated activity and pathways involved in immortalization, proliferation, and motility.

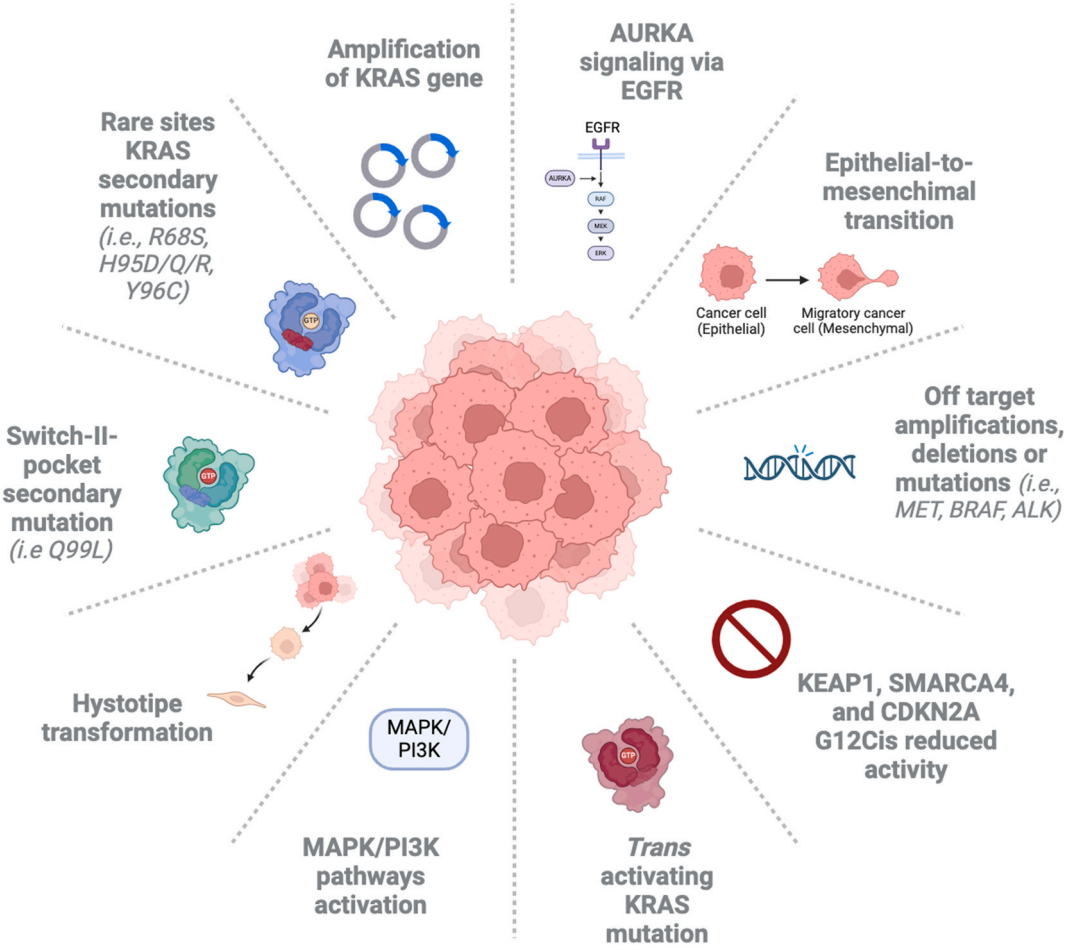

Fig. 2. Summary of mechanism of resistance to KRAS inhibitors exposure.

and a reasonable safety profile, remains a clinical challenge.

1.2. KRAS and tumor micro-environment (TME)

The understanding of the impact of KRAS on TME and on mechanisms of immune-evasion has recently become particularly relevant to the clinical management of NSCLC, given the significant role of ICIs in NSCLC treatment and the introduction of compounds targeting KRAS G12C (Fig. 3). In this context, Canon and colleagues described the ability of the G12Ci sotorasib (alone and in combination with an anti-PD-1 antibody) in promoting the recruitment of $CD8^+$ T cells in the TME of mouse $KRAS^{G12C}$ colorectal carcinoma, results not described with the anti-PD-1 alone, and to improve anti-PD-1 efficacy in this preclinical model [23]. These data have been recently confirmed for other KRAS inhibitors in different preclinical models, including a novel immunogenic model of KRASG12C-mutant LUAD [24]. Noteworthy, several independent groups have developed lines of evidence supporting the key role of KRAS-induced inflammation in carcinogenesis. KRAS is reportedly involved in cytokine production in macrophages (e.g., IL-6) supporting their polarization toward an anti-inflammatory (M2-like) phenotype, activation of transcription factors (e.g., STAT3 in $CD8^+$ T cells) and activation of the NLRP3 inflammasome [25,26]. Conversely, IL-8 via MAPK or PI3K pathways play an essential role in angiogenesis and endothelial cells recruitment, supporting tumorigenesis [27,28], and several preclinical models showed the importance of activation of NF-κB and IL-1 in inflammatory-mediated tumorigenesis [29,30]. The concurrent oncogene MYC/ RAS mutations are liable to pro-inflammatory, pro-angiogenic and immune-suppressive TME as described in lung cancer preclinical models [31].In addition to the pro-tumorigenic activity, KRAS is also involved in immuno-suppressive mechanisms, granting cancer cells the ability to evade the killing activity of $CD8^+$ T cells or NK cells. One of the most investigated mechanisms is the ability of KRAS to promote PD-L1 expression and consequently immunosuppressive functions, via MAPK, ERK and Akt/mTOR pathways [32–34]. PD-L1 indeed inactivates the detection and killing functions of tumor-specific T cells, reshaping the activity of the TME when KRAS induces its hyperexpression. Liu and colleagues demonstrated in a KRAS-mutant LUAD - mouse model an activity of anti-PD-L1 mAb and showed decreased expression of PD-L1 and increased infiltration of $CD8^+$ T cells compared with docetaxel-treated mice [35]. Finally, loss of function of *TP53* and *STK11/LKB1* are also involved in immune-escaping [36]. The complexity of the mechanisms in which KRAS is

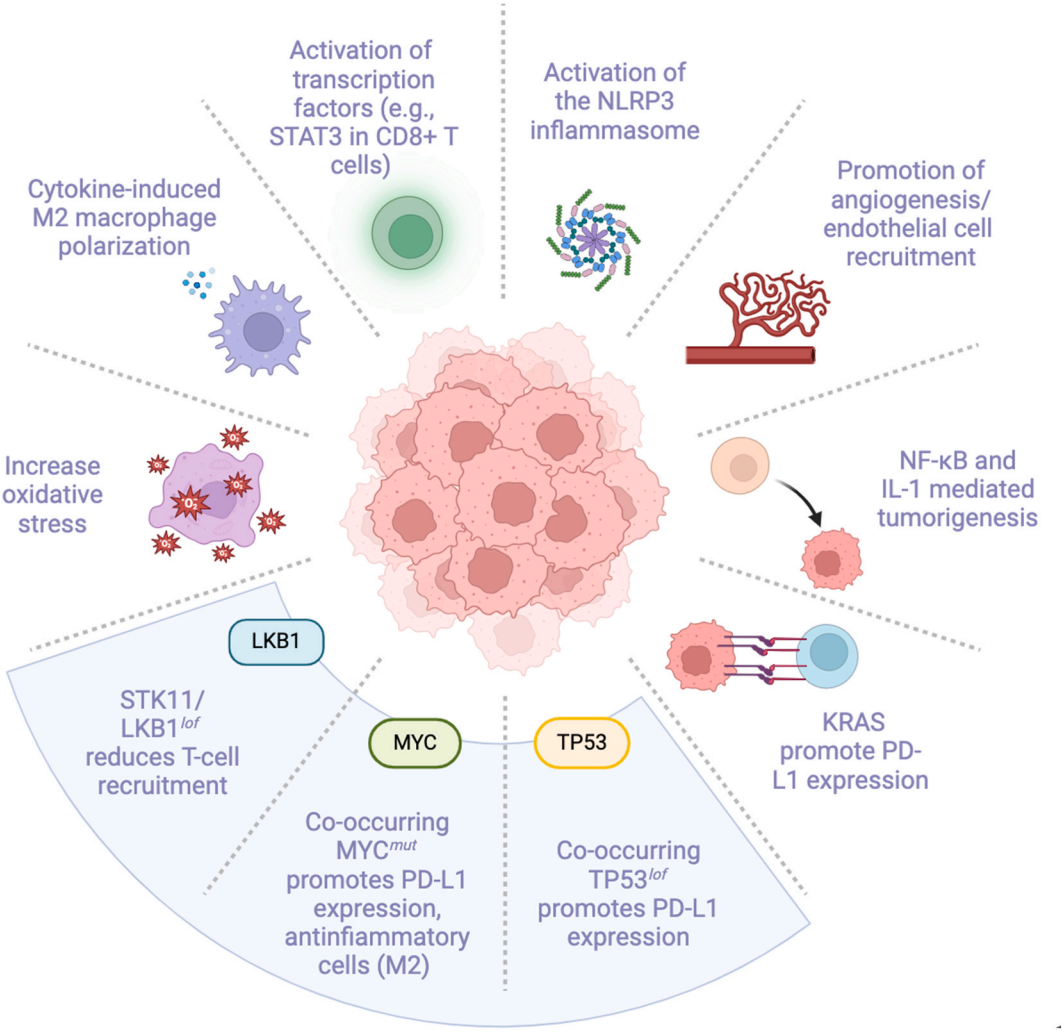

Fig. 3. Schematic representation of KRAS involvement in the TME. The upper part of the figure shows the summary of pro-inflammatory and pro-tumorigenesis mechanisms. The lower part of the figure (light violet) summarizes the involvement of co-occurring mutations and their ability to promote immune evasion with KRAS mutation. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

involved, and particularly the modulation of the peri-tumor inflammatory response, is evident and not completely well understood. Several retrospective analyses described in KRAS mutated patients a different performance of ICIs, with or without CT [37,38]. A glimmer of hope in understanding such intricate tangles as the treatment of patients mutated for KRAS comes from the recent presentation of *post-hoc* analysis of data from the POSEIDON trial. As previously suggested by similar analysis of the 9LA trial about KRAS/KEAP1/STK11 patients, the POSEIDON trial confirmed increased survival outcomes and response rates from the combination with anti-CTLA-4 and anti-PD-1 in addition to CT, with a reduction in the risk of death of around 50 % in all these subgroups. Several clinical trials are ongoing to explore the efficacy of combinations between KRAS inhibitors and numerous other molecules, including anti-PD-L1/PD-1 drugs (Table 1).

2. Conclusion

Mutant KRAS is extremely heterogeneous and can only be partially deemed a common target as EGFR. The precise identification of the single mutation in the naïve patient, as well as of any other pre-existing or subsequently arising co-mutations, could expand the range of drug combinations almost infinitely. The use of inhibitory strategies not directly targeting KRAS without neglecting the role of ICIs could bypass both the possible mechanisms of primary and acquired resistance, as allow the use of similar strategies in different KRAS point mutations.

Table 1
Summary table of major phase I-III on-going clinical trials with drugs or drug combinations aimed at KRAS G12C inhibition.

	TITLE OF THE STUDY	CLINICAL PHASE	NCT NUMBER
1	Carfilzomib in Combination with Sotorasib for the Treatment of Patients With KRAS G12C Mutated Advanced or Metastatic Non-small Cell Lung Cancer	Phase 1	NCT06249282
2	Study of RAS(ON) Inhibitor Combinations in Patients With Advanced RAS-mutated NSCLC	Phase 1 Phase 2	NCT06162221
3	A Study of LY3537982 Plus Immunotherapy With or Without Chemotherapy in Participants With Non-Small Cell Lung Cancer (NSCLC) With a Change in a Gene Called KRAS G12C	Phase 3	NCT06119581
4	AMG510 (Sotorasib) Plus Lenvatinib as Second-line Treatment in Patients With KRASG12C Mutant, Metastatic NSCLC	Phase 2	NCT06068153
5	JDQ443 for KRAS G12C NSCLC Brain Metastases	Phase 2	NCT05999357
6	A Study Evaluating Sotorasib Platinum Doublet Combination Versus Pembrolizumab Platinum Doublet Combination as a Front-Line Therapy in Participants With Stage IV or Advanced Stage IIIB/C Nonsquamous Non-Small Cell Lung Cancers (CodeBreaK 202)	Phase 3	NCT05920356
7	Trial of Two Adagrasib Dosing Regimens in NSCLC With KRAS G12C Mutation (KRYSTAL 21)	Phase 2	NCT05853575
8	Adagrasib in Combination With Nab-Sirolimus in Patients With Advanced Solid Tumors and Non-Small Cell Lung Cancer With a KRAS G12C Mutation (KRYSTAL -19)	Phase 1 Phase 2	NCT05840510
9	Ladarixin With Sotorasib in Advanced NSCLC	Phase 1	NCT05815173
10	A Study Evaluating the Safety, Activity, and Pharmacokinetics of Divarasib in Combination With Other Anti-Cancer Therapies in Participants With Previously Untreated Advanced or Metastatic Non-Small Cell Lung Cancer With a KRAS G12C Mutation	Phase 1 Phase 2	NCT05789082
11	A Study of GFH925 in Combination With Cetuximab in Previously Untreated Advanced NSCLC Harboring KRAS G12C Mutation	Phase 1 Phase 2	NCT05756153
12	Combination Therapies With Adagrasib in Patients With Advanced NSCLC With KRAS G12C Mutation	Phase 2	NCT05609578
13	A Study to Evaluate D-1553 in Combination Therapy in Non-Small Cell Lung Cancer	Phase 1 Phase 2	NCT05492045
14	SHP2 Inhibitor BBP-398 in Combination With Sotorasib in Patients With Advanced Solid Tumors and a KRAS-G12C Mutation	Phase 1	NCT05480865
15	Neoadjuvant KRAS G12C Directed Therapy With Adagrasib (MRTX849) With or Without Nivolumab	Phase 2	NCT05472623
16	An Open-label, Phase 2trial of Sotorasib in KRAS G12C-mutant Non-small-cell Lung Cancer(NSCLC) Patients and a Translational Study to Find Acquired Resistance Mechanism to Sotorasib	Phase 2	NCT05451056
17	Study of Efficacy and Safety of JDQ443 Single-agent as First-line Treatment for Patients With Locally Advanced or Metastatic KRAS G12C- Mutated Non-small Cell Lung Cancer With a PD-L1 Expression <1 % or a PD-L1 Expression ≥ 1 % and an STK11 Co-mutation.	Phase 2	NCT05445843
18	Clinical Trial of AMG510 in Stage III Unresectable NSCLC KRAS p.G12C Patients and Ineligible for Chemo-radiotherapy	Phase 2	NCT05398094
19	Study of Avutometinib (VS-6766) + Adagrasib in KRAS G12C NSCLC Patients	Phase 1 Phase 2	NCT05375994
20	A Study of JAB-21822 in Advanced or Metastatic NSCLC With KRAS p.G12C and STK11 Co-mutation and Wild-type KEAP1	Phase 1 Phase 2	NCT05276726
21	Study of JDQ443 in Comparison With Docetaxel in Participants With Locally Advanced or Metastatic KRAS G12C Mutant Non-small Cell Lung Cancer	Phase 3	NCT05132075
22	A Phase II Study of Neoadjuvant Sotorasib in Combination With Cisplatin or Carboplatin and Pemetrexed for Surgically Resectable Stage IIA-IIIB Non-Squamous Non-Small Cell Lung Cancer With a KRAS p.G12C Mutation	Phase 2	NCT05118854
23	Phase 1/2 Study of Avutometinib (VS-6766) + Sotorasib With or Without Defactinib in KRAS G12C NSCLC Patients	Phase 1 Phase 2	NCT05074810
24	JAB-21822 Activity in Adult Patients With Advanced Solid Tumors Harboring KRAS G12C Mutation	Phase 1 Phase 2	NCT05002270
25	Phase 2 Trial of Adagrasib Monotherapy and in Combination With Pembrolizumab and a Phase 3 Trial of Adagrasib in Combination in Patients With a KRAS G12C Mutation KRYSTAL-7	Phase 2 Phase 3	NCT04613596

Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Sara Fancelli: Writing – original draft, Conceptualization. **Giulia Petroni:** Writing – review & editing, Supervision, Resources. **Serena Pillozzi:** Writing – review & editing, Conceptualization. **Lorenzo Antonuzzo:** Writing – review & editing, Validation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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