


Extensive genomic analysis in patients with *KRAS*-mutated solid tumors shows high frequencies of concurrent alterations and potential targets but has limited clinical impact

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ABSTRACT

Background: This study aimed to investigate the distribution and frequency of concurrent alterations in different cancers across *KRAS* subtypes and in different *KRAS* subtypes across cancers, and to identify potentially actionable targets and patients who received targeted treatment matched to their genomic profile (GP).

Materials and Methods: In this descriptive and single-center study, we included 188 patients with solid tumors harboring *KRAS* mutations in codon 12, 13, 61, 117, or 146, referred to the Phase 1 Unit, Rigshospitalet, Copenhagen, Denmark from mid-2016 to 2020. Genomic co-alterations were detected with whole-exome sequencing, RNA sequencing, SNP array, and mRNA expression array on fresh biopsies. The study is part of the Copenhagen Prospective Personalized Oncology study (NCT02290522).

Results: The majority of patients had colorectal cancer (60.1%), non-small cell lung cancer (11.2%), or pancreatic cancer (10.6%). Most tumors were *KRAS*-mutated in codon 12 or 13 (93.7%) including G12D (27.1%), G12V (26.6%), G12C (11.7%), and G13D (11.2%). A total of 175 different co-alterations were found, most frequently pathogenic *APC* and *TP53* mutations (55.9% and 46.4%, respectively) and high expression of *CEACAM5* (73.4%). Different cancers and *KRAS* subtypes showed different patterns of co-alterations, and 157 tumors (83.5%) had potentially actionable targets with varying evidence of targetability (assessed using ESMO Scale for Clinical Actionability of molecular Targets). Of the 188 patients included in the study, 15 (7.4%) received treatment matched to their GP (e.g., immunotherapy and synthetic lethality drugs), of whom one had objective partial response according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

Conclusion: Performing extensive genomic analysis in patients with known *KRAS*-mutated solid tumors may contribute with information to the genomic landscape of cancers and identify targets for immunotherapy or synthetic lethality drugs, but currently appears to have overall limited clinical impact, as few patients received targeted therapy matched to their GP.

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Introduction

The *KRAS* gene is mutated in approximately 22% of all tumors [1], predominantly in pancreatic, colorectal, and lung carcinoma [2] with a mutation frequency of 90%, 40%, and 30%, respectively [3–6]. The *KRAS* protein is active when GTP-bound and mainly operates in the MAPK and PI3K pathways, which are involved in cell proliferation, growth, and survival [6].

The oncogenic activity of active GTP-*KRAS* comes from increased rate of nucleotide dissociation and/or decreased rate of hydrolysis of GTP to GDP and the most common mutations (at codon 12, 13, 61, 117, and 146) cluster around the nucleotide binding pocket [7,8].

Novel drugs targeting the *KRAS* mutation subtype G12C (e.g., adagrasib and sotorasib) work by locking *KRAS* in its inactive GDP-state [9]. Apart from G12C-selective inhibitors there are no effective *KRAS* targeted therapies available. Drug resistance to upstream and downstream inhibitors [10], such as anti-EGFR or anti-HER2 therapy [11–13] means few gain-of-function co-mutations can be targeted. This study aimed to investigate the potential benefits of extensive genomic analysis in patients with *KRAS*-mutated solid tumors. We examined the distribution and frequency of concurrent pathogenic mutations and other genomic alterations found in different *KRAS* mutation subtypes across histological cancer diagnoses and in different cancer diagnoses across *KRAS*

subtypes. We also identified potentially actionable targets and patients who received targeted therapy matched to their genomic profile (GP).

Methods and materials

Study design

This is a descriptive single-center study conducted at the Phase 1 Unit at the Department of Oncology at Rigshospitalet, Copenhagen University Hospital, Denmark.

Patients with advanced solid tumors, who have exhausted standard treatment options, can be referred to the Phase 1 Unit for extensive genomic tumor profiling. The GP is discussed at a multidisciplinary national tumor board meeting and potential treatment options are suggested based on targetable aberrations.

All patients with a GP from 1 July 2016 to 31 December 2020 harboring a *KRAS*-mutated tumor with subtype G12X, G13X, Q61X, K117X, or A146X were included. A total of 188 patients, corresponding to approx. 17% of all referrals in the same time period, were identified.

This study is a part of the Copenhagen Prospective Personalized Oncology (CoPPO, NCT02290522 [14]) study, which is conducted in accordance with the Declaration of Helsinki and has been approved by an institutional review board and the Regional Ethics Committee (Danish Ethical Committee, file number: 1300530) [15]. Written informed consent has been obtained from all study participants.

Clinical and genomic data

Study data were managed using REDCap electronic data capture tools [16,17] version 10.3.3. The genomic analyses were performed on either biopsy samples ($n = 170$, 90.4%), circulating tumor DNA (ctDNA) ($n = 14$, 7.5%), both ctDNA and biopsy ($n = 3$, 1.6%), or archived formalin-fixed, paraffin-embedded (FFPE) tissue ($n = 1$, 0.5%). Individual genomic reports based on analysis results from whole-exome sequencing (WES), RNA sequencing, SNP array, and mRNA expression array were provided by the Center for Genomic Medicine, Rigshospitalet, Denmark. The tumor specific variants were called and annotated by the software used at the time (either CLC workbench or GATK). Variants with an allele frequency down to 10% were assessed and used for further curation. Methods regarding genomic data processing have been reported in previous CoPPO articles [15,18]. The turnaround time from tumor sample to report was 4–6 weeks.

All reports were evaluated for co-alterations and actionability by board certified clinical oncologists at the Phase 1 Unit and were then recorded in REDCap. The recorded genomic alterations comprised all: (I) cancer-associated mutations (classified as either variant of unknown significance (VUS) or pathogenic) incl. high Tumor Mutational Burden (TMB) defined as >10 mut/Mb as defined by the Center for Genomic Medicine, corresponding to approx. 300 mutations (not exclusively missense mutations included) [19]; (II) fusions; (III) amplifications; (IV) biallelic deletions; (V) homologous recombination deficiency (HRD) [20]; and (VI) high expression of *CEACAM5*. All other expression

findings, loss of heterozygosity (LOH), and deletions were not recorded due to potential inconsistency over time and low possibility of targetability. However, we included the *PTEN* gene if deletion and/or LOH occurred concomitantly with a mutation, corresponding to *PTEN* loss (biallelic deletion). In the case of multiple genomic reports showing alterations co-occurring with a *KRAS* mutation in the same patient, all alterations (I–VI) were recorded, but the same alteration would only be recorded once to prevent duplicate entries.

Potentially actionable targets were assessed from a present-day perspective due to the ever-evolving understanding and definition of targetability. The term ‘actionable’ refers to the ability of the alteration to be targeted by an agent based on clinical or preclinical data.

All clinical data were retrospectively collected from electronic medical records.

Statistical analysis

Data were analyzed using R Studio version 1.2.5001 [21] and SPSS Statistics version 25 [22]. Continuous variables were summarized using mean, standard deviation, median, minimum, and maximum as appropriate. Categorical variables were summarized using number and percentage.

Results

Patient characteristics are presented in Table 1. The majority of patients had colorectal cancer (CRC; $n = 113$, 60.1%), non-small cell lung cancer (NSCLC; $n = 21$, 11.2%), or pancreatic cancer ($n = 20$, 10.6%).

KRAS subtypes

Codon 12 and 13 mutations accounted for 93.7% of all *KRAS* mutations (80.9% at codon 12 and 12.8% at codon 13). Across tumor types, G12D and G12V were the most frequent mutations (27.1% and 26.6%, respectively), followed by G12C (11.7%) and G13D (11.2%). The frequencies of *KRAS* mutation subtypes in CRC, NSCLC, pancreatic cancer, and all other cancers are outlined in Figure 1, and the distribution of all diagnoses and subtypes are listed in Supplementary Table 1.

Among the 188 patients, 64 (34.0%) had no known *KRAS* mutation upon referral. The majority of these tumors ($n = 56$, 87.5%) had not previously been analyzed for *KRAS* (all 113 CRCs had prior *KRAS* analysis). The remaining eight tumors (12.5%) were initially *KRAS* wild-type (wt) (CRC $n = 7$, neuroendocrine carcinoma $n = 1$). Of the seven *KRAS* wt CRC patients, six had received anti-EGFR therapy prior to referral to the Phase 1 Unit. The initial GP of another patient showed a *KRAS* wt, *BRAF* V600E mutated breast cancer and the patient received 64 weeks of *BRAF* targeted therapy (dabrafenib + trametinib). Upon progression, a new GP revealed presence of *KRAS* mutations (G12V and G12A).

Of the 124 patients with known *KRAS* mutation upon referral, 119 (96.0%) had the same *KRAS* mutation subtype in the GP as the one previously found (or a mutation in the

Table 1. Patient characteristics at date of referral to the Phase 1 Unit.

Characteristics	Included in KRAS study (n = 188)
Gender	
Female	99 (52.7%)
Male	89 (47.3%)
Age in years	
Mean (SD)	62.0 (10.3)
Median (range)	62.6 (20.6–83.4)
Years from primary cancer diagnosis to referral	
Mean (SD)	3.0 (3.1)
Median (range)	2.4 (0.2–26.5)
Years from advanced/metastatic disease to referral	
Mean (SD)	2.0 (2.3)
Median (range)	1.4 (0.4–26.5)
Number of metastatic sites	
Median (range)	2 (0–6)
Number of prior treatment regimens (from advanced disease to referral)	
Median (range)	3 (0–11)
Performance status (ECOG)	
0	80 (42.6%)
1	95 (50.5%)
2	7 (3.7%)
3	2 (1.1%)
Unknown value	4 (2.1%)
Cancer type	
CRC (rectal cancer n = 35, colon cancer n = 78)	113 (60.1%)
NSCLC (adenocarcinoma n = 20, squamous n = 1)	21 (11.2%)
Pancreatic cancer	20 (10.6%)
Neuroendocrine carcinoma	7 (3.7%)
Ovarian cancer	5 (2.7%)
Breast cancer	5 (2.7%)
Gastric/gastro-esophageal junction cancer	3 (1.6%)
Cancer of unknown primary origin	3 (1.6%)
Small cell lung cancer	2 (1.1%)
Biliary tract cancer	2 (1.1%)
Appendix cancer	2 (1.1%)
Bladder cancer	1 (0.5%)
Cervical cancer	1 (0.5%)
Endometrial cancer	1 (0.5%)
Head and neck cancer	1 (0.5%)
Small intestine cancer	1 (0.5%)

ECOG: The Eastern Cooperative Oncology Group performance status scale; SD: standard deviation; CRC: colorectal cancer; NSCLC: non-small cell lung cancer.

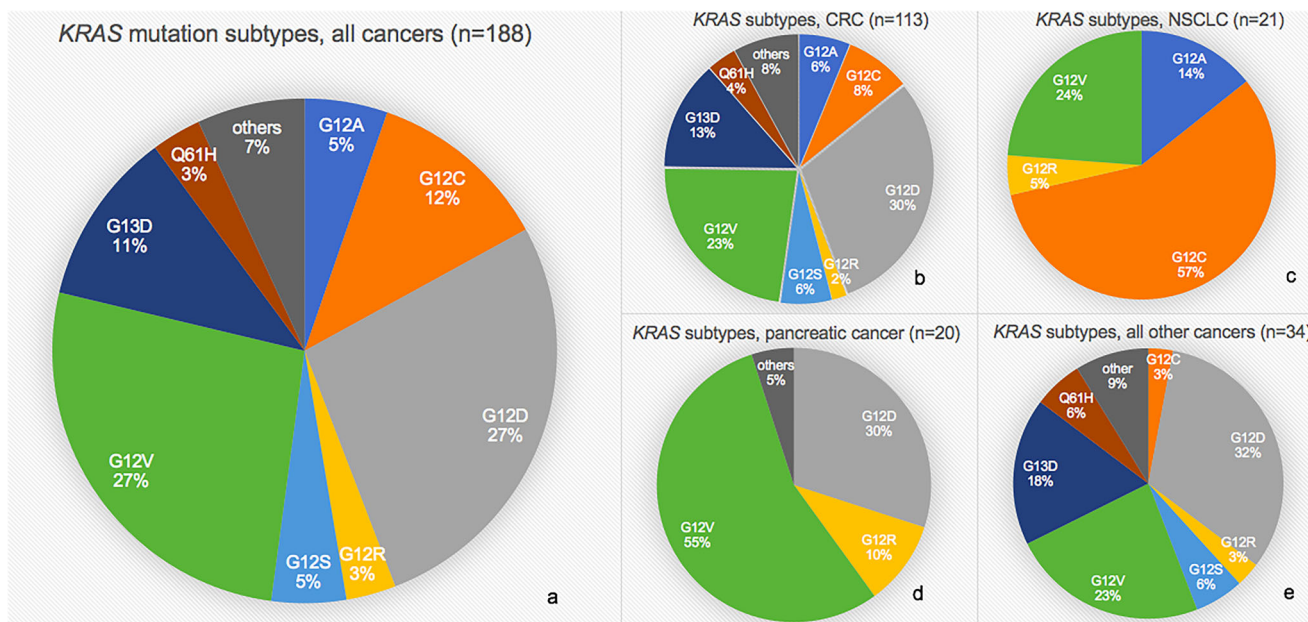


Figure 1. Pie charts of relative frequencies of different KRAS mutation subtypes among cohort. (a) All cancers. (b) Colorectal cancer (CRC). (c) Non-small cell lung cancer (NSCLC). (d) Pancreatic cancer. (e) All other cancers.

same codon if not specified further). Five tumors (4.0%) had a different subtype in the GP (Supplementary Table 2).

Co-occurring genomic alterations

In total, 175 different cancer-related co-occurring genomic alterations were recorded, with a median of four co-alterations per tumor. There were 164 (87.2%) tumors with at least one cancer-associated pathogenic co-mutation, and 138 tumors (73.4%) had high RNA expression of *CEACAM5*. HRD was found in 37 tumors (19.7%) and 13 tumors (6.9%) were TMB high (Supplementary Table 3).

The co-alterations present in >5% of CRCs, NSCLCs, pancreatic cancers, or all other cancers pooled together (across *KRAS* subtypes) included alterations in the genes *APC*, *ATM*, *BRCA1/2*, *CDKN2A*, *CCND1*, *ERBB2*, *FBXW7*, *GNAS*, *PIK3CA*, *RB1*, *SMAD4*, *STK11*, *TP53*, *KRAS*, *MDM2*, *MYC*, and *PTEN* (Figure 2(a)). The co-alterations present in >5% of tumors with *KRAS* mutations G12D, G12V, G12C, G13D, or all other subtypes pooled together (across cancers), included alterations in the genes *APC*, *ATM*, *BRCA2*, *CDKN2A/B*, *ERBB2*, *FBXW7*, *PIK3CA*, *SMAD4*, *STK11*, *TP53*, *KRAS*, *MYC*, and *PTEN* (Figure 2(b)).

A complete overview of the distribution and frequency of all the different co-alterations recorded are presented in Supplementary Tables 3 and 4, stratified by tumor type including all *KRAS* subtypes (Supplementary Table 3) and by *KRAS* subtype including all tumor types (Supplementary Table 4).

Potential targets and treatment

Potentially actionable targets were identified in 157 tumors (83.5%), of which 138 (73.4%) had high expression of *CEACAM5*, and 85 (45.2%) had other potential targets (Figure 3). ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) levels for all potential targets have been assessed and presented in Supplementary Table 5.

A total of 41 patients (21.8%) received treatment in the Phase 1 Unit (Figure 4). Of the 41 patients, 15 received targeted treatment matched to their GP, of whom one patient had objective partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.

The remaining 26 patients received non-matched therapy in early clinical trials. Notably, 145 patients (77.1%) did not receive treatment in the Phase 1 Unit, 120 of whom despite potentially actionable targets.

There were 44 patients (23.4%) who subsequently received standard systemic treatment at their local hospital, but most received palliative care. The median survival time from referral to the Phase 1 Unit was 5.7 months (Supplementary Table 6).

Discussion

In this descriptive study of 188 patients with *KRAS*-mutated solid tumors representing 16 cancer types, we investigated the distribution and frequency of *KRAS* subtypes, genomic co-alterations, and potential targets.

The majority (93.7%) was *KRAS*-mutated in codon 12 or 13, and subtype G12D and G12V were the most frequent across tumor types, consistent with other studies [2,7,23].

In NSCLC and pancreatic cancer, only codon 12 mutations were observed. Mutations outside codon 12 or 13 were only found in CRC. In concordance with this study, mutations in codon 13, 117, and 146 have been described as more common in CRC relative to NSCLC and pancreatic cancer. Furthermore, mutations in codon 117 and 146 have been described as nearly selective for CRC compared to all cancers [8].

Our study population was highly selected, comprising patients with advanced disease, who had received several treatment regimens prior to referral to the Phase 1 Unit, and who were still in good general performance. This may explain the relatively small NSCLC and pancreatic cancer subgroups (21 and 20 patients, respectively), and the *KRAS* mutation subtype frequencies found in this study may therefore not represent the *KRAS* mutation frequencies in the general cancer population. Nonetheless, we found cancer-specific distribution of the various *KRAS* mutation subtypes, similar to other studies [2,4,23].

We recorded 175 different cancer-related co-alterations. The most frequent were pathogenic mutations in the *APC* and *TP53* gene and high expression of *CEACAM5*. Pathogenic *APC* mutations and high expression of *CEACAM5* were most frequent in CRC (85.8% and 92%, respectively). Consistent with these findings, other studies have found co-occurrence of *APC* and *KRAS* mutations in 80% of CRCs [23], and high expression of *CEACAM5* in 90% of CRCs (*KRAS* status unknown) [24]. In our study, co-occurring *TP53* mutations appeared more common in CRC (63.7%) and pancreatic cancer (75%) compared to NSCLC (23.8%). Similarly, another study showed that *KRAS* mutations often occur together with *TP53* in CRC, pancreatic cancer, and NSCLC, although at frequencies of 40%, 80%, and 40%, respectively [23].

This study did not distinguish between left- and right-sided colon cancers, which have previously been shown to differ in regards to mutations and epigenetic changes [25,26]. Thus, as the distribution of the colon cancers was not known and which could potentially impact the co-alterations observed, we decided to pool colon and rectal cancers together. However, as the majority of patients had CRC (60.1%) it would have been relevant to compare diagnostic subgroups as the importance of *KRAS* subtypes and concurrent genomic alterations might be different in different diagnostic subgroups.

Mutations in the tumor suppressor genes *APC* and *TP53* are frequent alterations in human cancers [27,28], but cannot yet be targeted with therapy. High expression of *CEACAM5* was considered an actionable target as several trials with bispecific antibodies targeting *CEACAM5* were accruing patients with high *CEACAM5* expression at our facility during the study period. HRD, TMB high, loss of *PTEN*, pathogenic mutations in *FBXW7*, *PIK3CA*, *ATM*, *BRAF* (V600E), *ERBB3*, and *IDH1*, and amplifications of *ERBB2*, *EGFR*, *CDK4*, *MDM2*, and *MET* were also considered actionable, all of which were found in this study, with ESCAT levels ranging from I-A to IV (Supplementary Table 5).

Potentially actionable targets were identified in 83.5% of the patients. This is numerically higher than the 76.5% (352 of 460 GPs) previously reported by our facility (CoPPO) [15],

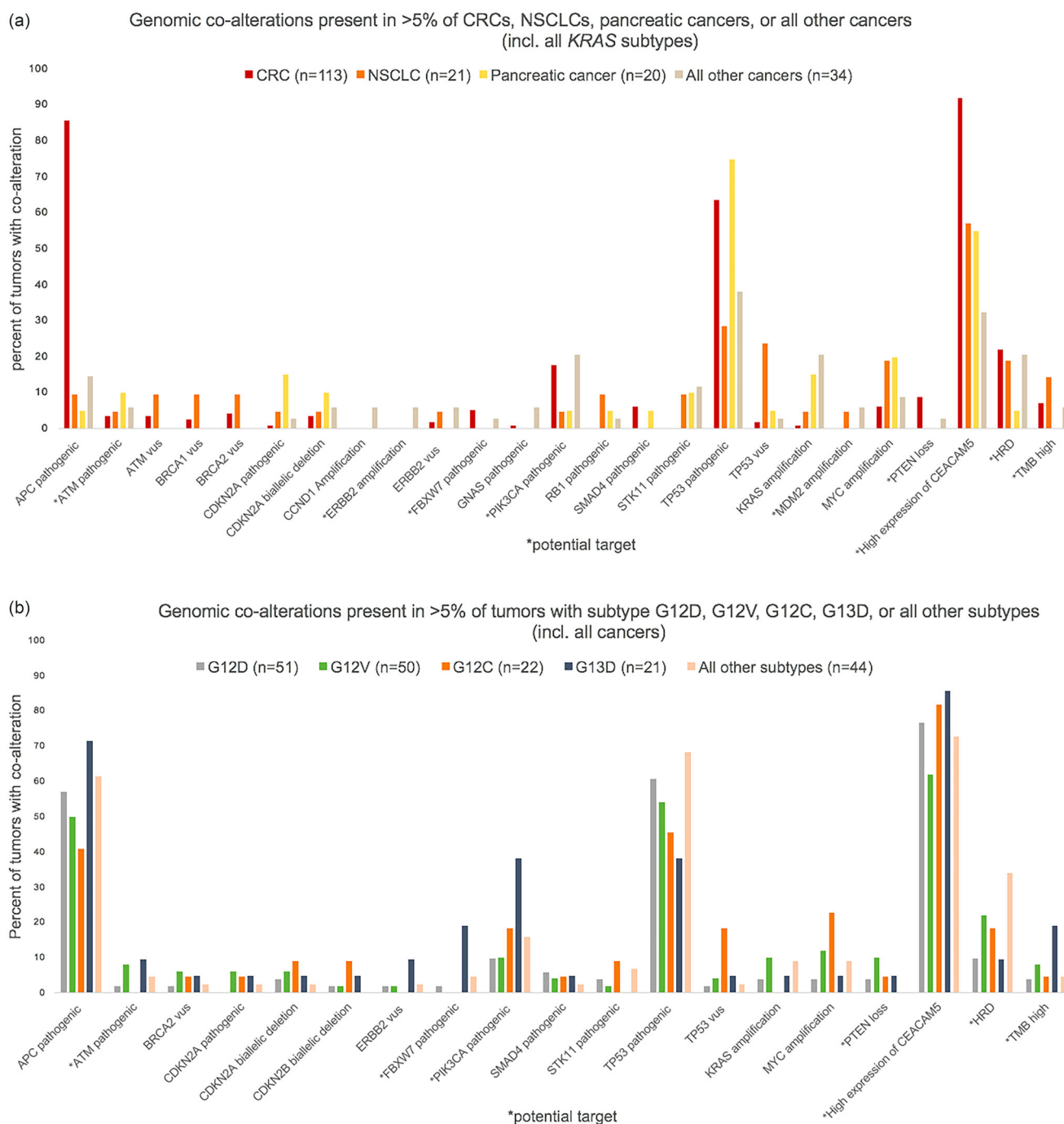


Figure 2. Bar chart of relative frequencies of co-occurring genomic alterations in different tumors. (a) In colorectal cancer (CRC), non-small cell lung cancer (NSCLC), pancreatic cancer, or all other cancers across all *KRAS* subtypes. (b) In tumors with *KRAS* mutation G12D, G12V, G12C, G13D, or all other subtypes across all cancers. Only alterations present in >5% of tumors are shown. Pathogenic: pathogenic mutation; vus: variant of unknown significance; HRD: homologous recombination deficiency; TMB: tumor mutational burden. *PTEN* loss include *PTEN* biallelic deletions and *PTEN* pathogenic mutation+*PTEN* deletion and/or loss of heterozygosity.

which could be explained by dynamics in the definition of targets and advances in precision oncology. However, a considerable smaller proportion of patients received targeted treatment matched to their GP in this study (7.4%) compared to 22% in the previous study by CoPPO, which included all patients with solid tumors referred to the Phase 1 Unit 2013–2017 [15]. The response rate was also lower in this study: 0.5% vs. 3.3% (1 PR of 188 GPs vs. 15 PRs of 460 GPs), and 6.7% vs. 14.9% (1 PR of 15 treated matched to GP vs. 15 PRs of 101 treated matched to GP). This could be due to the

fact that targeting alterations upstream or downstream of the *KRAS* signaling pathway are without significant success and the absence of other actionable driver mutations in the study population [29].

In our study, 26 patients (13.8%) received non-matched therapy in early clinical trials. The majority (77.1%) did not enroll in any trials in Phase 1, most likely due to performance decline or non-eligibility in clinical trials.

Despite the high number of potentially actionable targets, few patients with *KRAS*-mutated tumors received targeted

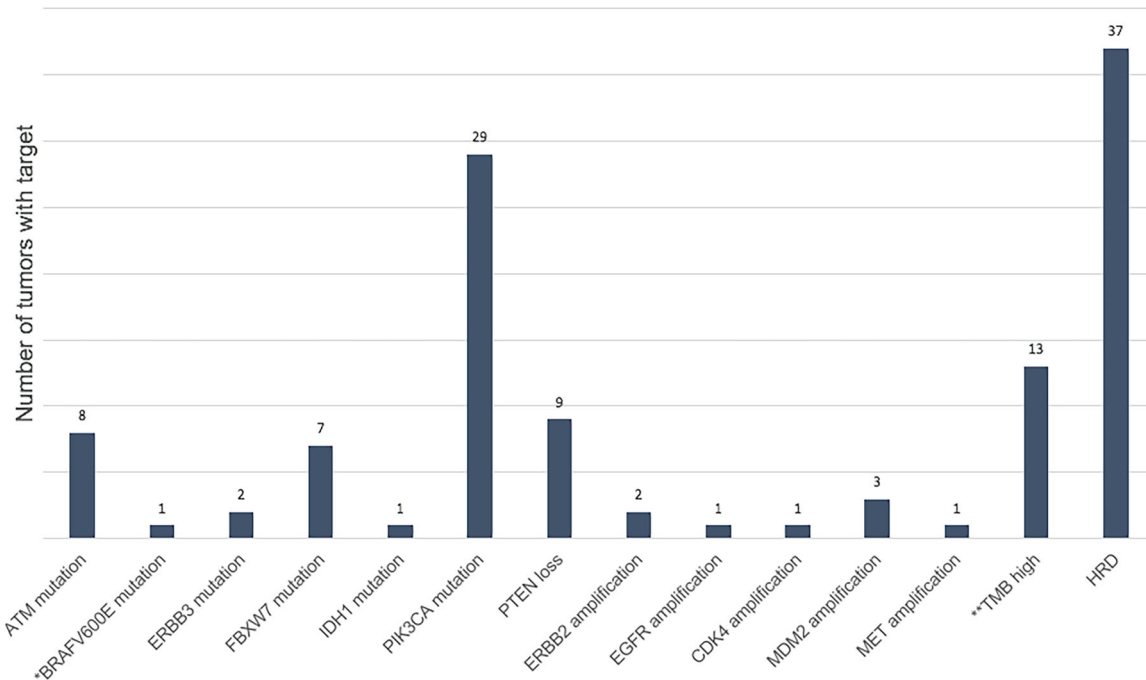
Prevalence of potential targets (excl. high expression of *CEACAM5*)

Figure 3. Prevalence of potential targets in 85 tumors with targets other than high expression of *CEACAM5*. *The patient with breast cancer who received BRAF targeted therapy. **With/without pathogenic mutations in mismatch repair genes. 62 tumors had one target, 17 tumors had two, five tumors had three and one tumor had four targets. HRD: homologous recombination deficiency; TMB: tumor mutational burden. *PTEN* loss include *PTEN* biallelic deletions and *PTEN* pathogenic mutation+*PTEN* deletion and/or loss of heterozygosity.

therapy matched to their genomic profile. Although *KRAS* mutations do not per se exclude other actionable driver mutations, these co-existing driver mutations are rare and often not actionable due to concomitant *KRAS* mutation (e.g., *ERBB2* amplification or *BRAF* mutations). The co-occurring targets at DNA or chromosomal level are mainly characterized by being loss-of-function alterations (e.g., *ATM* and HRD) constituting a potential target for synthetic lethality drugs (PARP and ATR inhibitors) or TMB-high status constituting a potential target for immune checkpoint inhibitors.

Many genomic alterations co-occur with *KRAS*, and although some may not be currently targetable, the genomic landscape is changing. Genomic profiling of *KRAS*-mutated tumors contributes to this research and may uncover new treatable targets, especially loss-of-function mutations inferring targets of synthetic lethality and/or increasing our knowledge of resistance mechanisms, ultimately benefitting these patients. An example of the latter, is the breast cancer patient who received BRAF targeted therapy due to an activating *BRAF* mutation (V600E) found in the initial GP, and whose tumor developed *KRAS* mutations upon progression, indicating well-known resistance mechanisms [30,31].

Another potential benefit of performing extensive genomic analysis in *KRAS*-mutated solid tumors is the prognostic and treatment-predictive information which may be derived from *KRAS* subtypes and co-occurring alterations [32–35]. Recent data from KRYSTAL-1, showed an even greater response to the *KRAS* G12C inhibitor adagrasib in patients with *KRAS*-mutated NSCLC, whose tumor also had a concurrent *STK11* mutation [36]. In our study, two patients could potentially have had increased benefit from receiving adagrasib. These

patients had *KRAS* G12C mutated NSCLCs and *STK11* co-mutations, one of which was pathogenic, and one was a VUS.

As G12C-selective inhibitors are being introduced, with observed objective response in NSCLC, CRC and other *KRAS*-mutated solid tumors [37–39] and with the recent FDA approval of sotorasib in NSCLC, the possibility of combined targeted therapy arises. At present time, however, the outcome of combining *KRAS* G12C inhibitors with other treatments based on molecular tumor profiling is unknown. Double-targeted therapy is currently being investigated in clinical trials such as combining anti-EGFR therapy with a G12C inhibitor for *KRAS* G12C mutant CRC (NCT04793958), and combining immune checkpoint inhibitors with a G12C inhibitor for *KRAS* mutant solid tumors (NCT04699188).

A definite strength of this study is the single-center design with uniformity and continuity in interpretation and decision making of each GP. In 15 cases, genomic analysis was presumably performed on an assay with less coverage of the genome, no RNA expression and less possibility of detecting chromosomal aberrations (14 ctDNA and one FFPE) as biopsy was not possible or contained normal tissue. These GPs may therefore have presented with fewer co-alterations.

There is no clear definition of what constitutes a potential target, and far from all target-drug combinations have the same therapeutic potential [40]. We included several potential targets with varying evidence of targetability, but the list of potential targets is not complete and will differ from site to site.

In conclusion, we found different patterns of *KRAS* mutation subtypes in different cancers, and varying frequencies of known genomic alterations co-occurring with *KRAS* in

Patients treated according to genomic profile

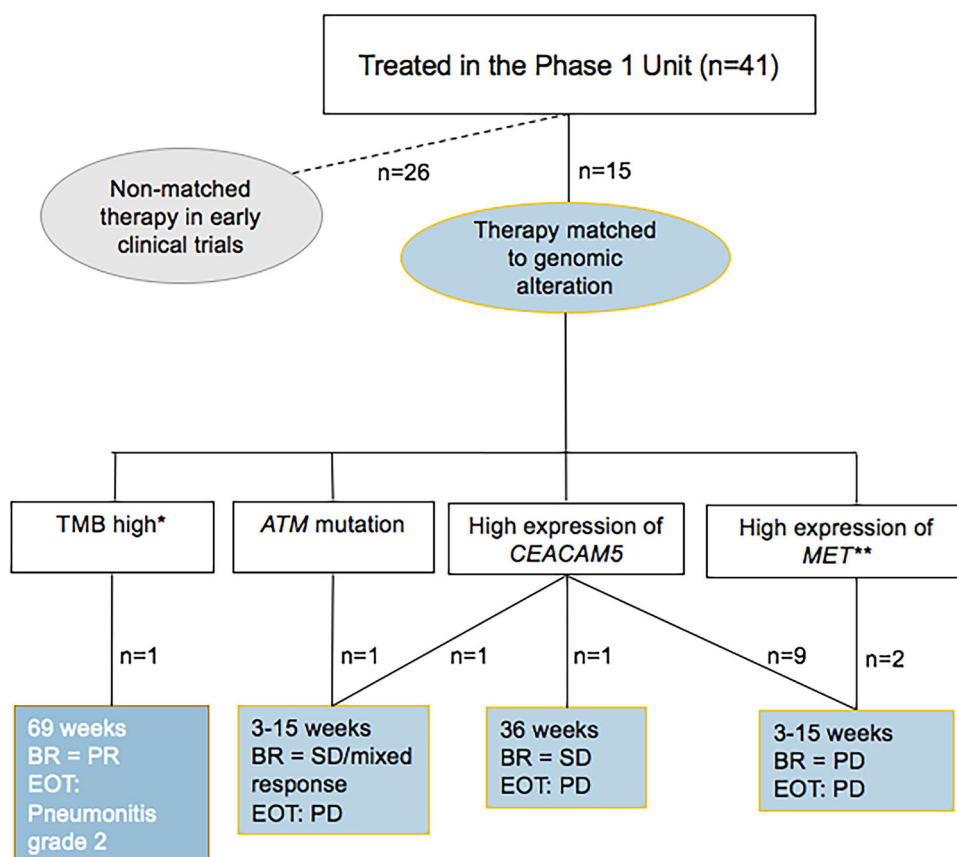


Figure 4. Patients treated according to genomic profile. *The patient received pembrolizumab based on high tumor mutation burden (TMB high). **Considered an actionable target at time of treatment. BR: best response according to RECIST 1.1; SD: stable disease; PR: partial response; PD: progressive disease; EOT: reason for end of treatment.

different cancers across subtypes and in different subtypes across cancers. The majority of patients had one or more potential targets but only a small percentage of the patients received targeted treatment matched to their genomic profile indicating limited clinical benefit from the analyses at present time.

The genomic landscape is continuously evolving and molecular characterization of concurrent alterations and potential targets as provided by our study will provide insight and add knowledge to this field. Furthermore, as KRAS G12C inhibitors are being introduced and an increasing number of loss-of-function alterations emerge as potential druggable targets in the synthetic lethality or functional restoration setting, the benefits of performing extensive genomic analysis in KRAS-mutated solid tumors may increase in the future.

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Authors' contributions

Guarantor of integrity of the entire study: KSR, UL. Study concepts and design: ICJ, IS, MH, UL, KSR. Literature research: ICJ, IS, KSR, MH, CQ.

Clinical studies: IS, MH, CQ, KSR, UL. Experimental studies/data analysis: ICJ, LB. Statistical analysis: ICJ, IS, KSR. Manuscript preparation: All authors. Manuscript editing: All authors.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

Data that underlie the results reported in this article can be made available upon reasonable request to the corresponding author, and will require the completion of a data processing agreement.

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