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Emerging personalized approaches for the management of advanced urothelial carcinoma

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Abstract

Urothelial carcinoma of the bladder comprises a spectrum of illnesses ranging from nonmuscle-invasive to muscle-invasive to advanced/metastatic disease. Each of these clinical states is characterized by a unique pathogenesis, prognosis and approach to treatment. However, given the heterogeneity of urothelial carcinoma, differences in biology and outcomes exist not only among these clinical states but also within each state. Personalized medicine, also commonly referred to as individualized or stratified medicine, offers the potential to optimize treatment for a given patient, based on the ability to accurately predict prognosis, response to treatment and tolerability of treatment. This review will discuss recent efforts, current challenges and future opportunities, for the personalized management of urothelial carcinoma.

Keywords

biomarker; bladder cancer; chemotherapy; neoadjuvant therapy; personalized medicine; urothelial carcinoma

Urothelial carcinoma (UC) is a chemosensitive neoplasm. The use of cisplatin-based combination chemotherapy has been shown to improve survival in both the perioperative and advanced disease settings. However, while the advances resulting from combination cisplatin-based chemotherapy in UC are clinically meaningful, the overall impact on this disease has been modest. Current therapies are particularly limited by extreme heterogeneity in patient outcomes and responses to treatment. Only subsets of patients derive benefit from particular systemic treatment regimens, and some patients experience severe treatment-related toxicities despite the lack of any appreciable benefit. The ability to individualize therapy by refining prognosis, and predicting treatment response, may allow more rational deployment of the current anti-cancer armamentarium and optimize patient outcomes. This review will describe the recent attempts to usher in the age of personalized cancer medicine in the care of patient with UC. While there are many opportunities to personalize

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management of noninvasive UC, given differences in pathogenesis and natural history, the current review will focus on invasive/advanced disease.

The pathogenesis of UC

Localized UCs has historically been referred to as either superficial or invasive, separating cancers which were confined to the either bladder mucosa or submucosa from those that invaded the bladder muscle. Currently, the term non-invasive is preferred instead of superficial in order to better capture the sometimes aggressive features of subsets of these tumors. Multiple molecular pathways have been implicated in the development of UC. However, two major pathways appear to play a role in the development of distinct clinical phenotypes: noninvasive tumors, which tend to recur but not invade the bladder wall, and tumors which invade the bladder wall and metastasize (Figure 1). These former, low-grade and noninvasive tumors, frequently demonstrate constitutive activation of the RAS-MAPK pathway, with activating mutations in *HRAS* and *FGFR3* genes. By contrast, high-grade cancers, both nonmuscle-invasive and muscle-invasive, demonstrate frequent alterations in *TP53* and *RB* genes and pathways [1]. Additional mutations, known to play a role in driving growth and progression of other solid tumors, have recently been identified in small subsets of invasive UC including KRAS and PIK3CA mutations [2]. In addition, loss of the tumor suppressor PTEN has been implicated in the pathogenesis of UC in mouse models [3]. Identification of these altered pathways is not only important in understanding the pathogenesis of UC, but also permits rational approaches to drug development, targeting the relevant pathways in given individuals.

Opportunities for personalized medicine in the management of muscle-invasive bladder cancer

Radical cystectomy with pelvic lymph node dissection is the standard approach for the management of patients with muscle-invasive bladder tumors. The probability of cure after surgery for muscle-invasive UC is associated with the pathologic stage, the ‘quality’ of surgery including margin status and extent of lymphadenectomy, and the use of perioperative chemotherapy. In a series of 1054 patients who underwent radical cystectomy at a single institution, the 5-year disease-free survival for patients with node-negative organ-confined disease was >80%. However, patients with lymph node involvement had a 5-year disease-free survival of only 35% [4].

Given the poor outcomes in patients with locally advanced disease, several studies have explored the integration of perioperative chemotherapy. Two large studies have established neoadjuvant cisplatin-based chemotherapy as a standard approach in muscle-invasive bladder cancer. The Southwest Oncology Group 8710 randomized patients with muscle-invasive bladder cancer to radical cystectomy alone (154 patients) compared with three cycles of methotrexate, vinblastine, doxorubicin and cisplatin MVAC followed by radical cystectomy (153 patients) [5]. At a median follow-up of 8.7 years, improvements in median survival (77 compared with 46 months; $p = 0.06$) and 5-year survival (57% compared with 43%; $p = 0.06$) favored the use of neoadjuvant arm. A Medical Research Council trial randomized 976 patients with muscle-invasive bladder cancer randomized patients to

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neoadjuvant cisplatin, methotrexate and vinblastine (CMV) (491 patients) versus local therapy alone (485 patients) [6]. An improvement in survival was observed for patients who received neoadjuvant chemotherapy (HR 0.84; 95% CI: 0.72–0.99; p = 0.037). Trials exploring adjuvant chemotherapy have been less compelling, but have generally been small, underpowered and utilized suboptimal chemotherapy regimens.

Because a large proportion of patients with muscle-invasive bladder cancer are cured with surgery alone (~50%), and only a subset benefit from the addition of neoadjuvant chemotherapy (approximately 5–10% absolute survival benefit), there is a crucial need for personalized approaches to identify patients who require integration of neoadjuvant therapy and to select patients likely to benefit from integration of particular drugs. A combination of routine clinical and pathologic variables may enhance the ability of individualize risk predictions, such as with the use of bladder cancer risk nomograms [7,101]. However, biomarkers offer the promise of capturing the heterogeneity in prognosis and outcomes not sufficiently captured with routine clinical and pathologic variables alone. Indeed, multiple studies have explored genes and gene panels in an attempt to improve prognostication in patients with clinically localized disease [8,9]. For example, studies have demonstrated that overexpression of four genes (*JUN*, *MAP2K6*, *STAT3* and *ICAM1*), molecules associated with cell survival (Bcl-2, caspase-3, p53 and survivin) and insensitivity to antigrowth signals (p53, p21, p16 and pRB) are correlated with poor outcomes following cystectomy [10–12]. Unfortunately, these tools have not yet been extensively analytically or clinically validated, and as a result have not been integrated into routine clinical practice.

A retrospective analysis demonstrated that immunohistochemical detection of p53 (a surrogate for mutant p53 status given the longer half-life than the wild-type protein) significantly correlated with a higher likelihood of recurrence after cystectomy [13]. Additional data from a retrospective trial of adjuvant cisplatin-based chemotherapy suggested that the benefit of adjuvant chemotherapy was restricted to patients with altered p53 status [14]. These data led to the design of a prospective trial that enrolled patients with pT1-T2 N0 bladder cancer status post cystectomy who consented for p53 analysis of their tumor specimen [15]. Patients with 10% nuclear positivity by immunohistochemistry of p53 were randomized to three cycles of adjuvant MVAC, while patients with wild-type p53 were observed. This study was designed to detect a 20% absolute decrease in recurrence rate at 3 years, but closed early when the results of a preplanned interim analysis after randomization of 110 patients suggested that the probability of achieving a significant difference in the time to recurrence in the randomized population was highly unlikely. In addition, the prognostic significance of p53 testing was not validated in this trial, highlighting the importance of prospective validation of retrospective studies.

Personalized medicine in the management of advanced/metastatic UC

The MVAC regimen, developed in the 1980s, represented a significant advance in the management of patients with meta-static bladder cancer [16]. MVAC was subsequently compared with single-agent cisplatin and various multidrug regimens, and based on superiority in randomized trials, was adopted as a treatment standard. However, despite the improvements with MVAC, median overall survival of patients with metastatic bladder

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cancer remained approximately 12–13 months, and this treatment regimen was associated with multiple toxicities. In an effort to improve the efficacy and tolerability of treatment, a landmark Phase III trial randomized 405 patients with metastatic urothelial carcinoma to gemcitabine plus cisplatin (GC) versus MVAC [17]. This trial demonstrated that the median overall survival was similar on both arms (MVAC: 15.2 months vs GC: 14 months; HR: 1.04; 95% CI: 0.82–1.32; p = 0.75). However, the GC arm was associated with a much more favorable toxicity profile. While the GC regimen represented an advance in terms of tolerability, despite attempts to build on this regimen [18], there have been no improvements in efficacy of treatment for advanced UC since the MVAC regimen was introduced.

Given that multiple chemotherapeutic agents, and 'targeted' therapies, have anti-tumor activity only in a subset of patients with bladder cancer, biomarkers predictive of response to therapy represent a major goal for personalized cancer medicine. A limited number of prospective studies in advanced urothelial cancer, thus far, have assigned therapy based on the presence or absence of a particular biomarker.

The EGF family of receptors has been implicated in the pathogenesis of UC, forming the rationale for pursuing therapeutic strategies targeting this pathway in advanced disease [19–21]. A Phase II trial of chemonaive patients with metastatic bladder cancer explored the combination of gemcitabine, carboplatin, paclitaxel, plus the anti-human EGF receptor 2 (HER-2) monoclonal antibody trastu-zumab. For enrollment on this trial, patient's tumors were required to have HER-2 overexpression by immunohistochemistry, *HER2* gene amplification and/or elevated serum HER-2. Notably, the overall response rate with this regimen was 70%. The contribution of trastuzumab to these results is unclear, and this regimen has not been moved forward for more definitive testing.

A Phase II study explored lapatinib, a dual HER-2/EGFR receptor pathway inhibitor, as second-line therapy in patients with metastatic UC. Patients were eligible provided that their tumors had 1^+, 2^+ or 3^+ expression of either EFGR or HER-2 by immunohistochemistry [22]. An objective response to treatment was observed in 1.7% (95% CI: 0.0–9.1%) of patients. However, 18 patients (31%; 95% CI: 19–44%) achieved stable disease. Clinical benefit with this regimen, defined as either an objective response or stable disease, was found to be correlated with EGFR overexpression and to some extent, HER-2 overexpression.

Another Phase II trial exploring lapatinib utilized a novel trial design focused on the putative predictive biomarker, rather than the specific tumor type [23]. Patients eligible for this study could have a wide variety of metastatic solid tumors (including bladder, endometrial, ovarian and gastric cancers) provided tumor tissue tested centrally demonstrated *HER2* gene amplification by FISH. Unfortunately, this trial was closed early due to poor accrual. Of the 33 patients with metastatic bladder cancer tested, 12 patients had *HER2* amplification by FISH, none of whom achieved an objective response to treatment [24]. These trials, which all utilized inhibitors of the same pathway, but different tests and 'cutoffs' for the putative predictive biomarkers, highlight many of the challenges of drug development in the era of targeted therapeutics.

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Activating mutations in *FGFR3* are present in a large proportion of noninvasive UC. However, recent studies have demonstrated that *FGFR3* mutations are also present in 10–20% of muscle-invasive UC specimens, leading to intense interest in exploring FGFR3 inhibition as a therapeutic strategy in UC, in an effort to recreate the successes achieved with targeting oncogenic mutations in other solid tumors [2]. Dovitinib is a small molecule inhibitor of several tyrosine kinase receptors, including the VEGF receptor and FGFR3, which has demonstrated inhibition of tumor growth and proliferation in UC models selected for the presence of FGFR3 activating mutations or protein over-expression. A multicenter, two-stage, open-label Phase II trial is currently evaluating the safety and efficacy of dovitinib in patients with advanced UC who have progressed despite prior systemic therapy [25]. In this trial, 40 patients will be enrolled into two groups of 20, based on the presence or absence of mutation in the *FGFR3* gene. The two groups will be recruited and analyzed independently and if at least two patients respond in either group, an additional 20 patients will be enrolled in that group. The results of this important trial, the first to enroll patients with advanced urothelial carcinoma based on the presence of an activating oncogenomic mutation, are anxiously awaited.

Future approaches to personalized medicine in UC

Because UC is a chemosensitive neoplasm, yet only a fraction of patients respond to a given chemotherapeutic regimen, there has been interest in developing tools to allow more rational use of the existing armamentarium of cytotoxics. One such approach has involved evaluating assessment of the levels of DNA-repair genes, or their protein products, in tumors, based on the notion that tumors with higher levels of DNA-repair genes may be more resistant to therapy. Excision repair cross complementing 1 (ERCC-1) is a critical regulator in nucleotide excision repair and its expression has been correlated with outcomes to cisplatin-based chemotherapy in various solid tumors [26–31]. RRM1, the regulatory subunit of ribonucleotide reductase, has been also implicated in carcinogenesis and tumor progression of non-small-cell lung cancer [32], and in addition predicted response to platinums and gemcitabine [33]. In a retrospective analysis, levels of the DNA-repair genes *ERCC1*, *RRM1*, *BRCA1* and caveolin-1, were evaluated in tumor tissue from 57 patients with bladder cancer treated with cisplatin-based combination chemotherapy [34]. The median survival was significantly higher in patients with low *ERCC1* levels (25.4 vs 15.4 months; $p = 0.03$). However, development of *ERCC1* as a widely available predictive biomarker has been hampered by difficulties with assay reproducibility, particularly at the protein level [35].

Given the molecular complexity of solid tumors, reliance on a single gene or protein as a predictive biomarker for response to cytotoxic chemotherapy is unlikely to yield substantial improvements in patient selection. Alternatively, expression profiling of thousands of genes may better capture the heterogeneity of responses to therapy. Indeed, ‘signatures’ of response to platinum-based chemotherapy based on gene expression profiles have been generated and correlated with clinical outcomes in patients with bladder cancer [8,36,37]. This approach is promising, but the predictive signature is limited to the particular treatment regimen evaluated in the study in which the signature was generated. As a result, new signatures must be developed for each new treatment regimen entering clinical use, and

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these signatures cannot be used to aid in the development of novel drugs that have not yet been explored in human studies.

In an effort to overcome many of the limitations of this conventional approach to treatment-predictive gene expression profile development, a novel bioinformatic approach known as Coexpression Extrapolation or COXEN was developed [38]. COXEN utilizes publicly available data regarding gene-expression profiling and drug sensitivity from the NCI-60 panel of tumor cell lines as a 'Rosetta Stone' to predict chemosensitivity of gene-expression profiled bladder cancer samples using a computational algorithm. Perhaps most remarkably, the NCI-60 panel does not contain any bladder cancer cell lines, but the gene expression profiles generated across the cell lines included has still been able to predict responses when applied to human bladder cancer specimens in retrospective studies. The COXEN methodology has also been utilized to successfully predict responses to breast and ovarian cancers in retrospective studies. The COXEN approach can be utilized to predict responses to multiagent regimens, by combining data regarding single agents, and has been utilized successfully to identify novel agents with activity in UC. A study is currently being planned to prospectively evaluate the COXEN approach for selection of second-line chemotherapy for patients with metastatic UC.

Personalized cancer care via profiling of tumor oncogenomics is best exemplified by the emerging treatment approach to advanced non-small-cell lung cancer. Identification of activating mutations *EGFR* and *ALK* have changed the treatment paradigm, pairing specific therapies to the presence of these aberrations [39,40]. Several groups evaluated UC samples for particular somatic mutations and these results have been cataloged in various databases including the Catalog of Somatic Mutations in Cancer [102]. However, given the distinct pathways of pathogenesis of UC, and corresponding clinical phenotypes, knowledge of the genomic profiles of non-invasive versus invasive tumors is necessary to identify targets relevant for therapeutic strategies in these particular clinical states. As a result, recent efforts have sought to profile both noninvasive and invasive samples, and samples of varying grades, for a variety of known cancer-related mutations (Table 1). In the most comprehensive analysis published to date, Sjödahl *et al*. performed mutation analyses of 16 genes (*FGFR3*, *PIK3CA*, *PIK3R1 PTEN*, *AKT1*, *KRAS*, *HRAS*, *NRAS*, *BRAF*, *ARAF*, *RAF1*, *TSC1*, *TSC2*, *APC*, *CTNNB1* and *TP53*) in 145 cases of UC [41]. This study identified that *FGFR3* and *PIK3CA* mutations were positively associated, and were identified more commonly in noninvasive low-grade tumors. Furthermore, the potential importance of APC signaling was identified as 6% of the investigated tumors either demonstrated inactivating *APC* or activating *CTNNB1* mutations. The mTOR regulatory tuberous sclerosis complex genes (*TSC1* and *TSC2*) were found to be mutated at a combined frequency of 15%. This study highlights the feasibility of potential therapeutic target identification by profiling individual UC tumors for know cancer-related somatic mutations, and future efforts will focus on pairing these aberrations with appropriate therapeutic agents.

Iyer *et al*. recently demonstrated the potential clinical relevance of oncogenic mutations in urothelial cancer [42]. In a study of everolimus as second-line therapy for patients with metastatic urothelial cancers, these investigators had previously demonstrated that a small number of patients achieved tumor regression. Notably, whole-genome sequencing of

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tumors from patients treated on this study revealed that the presence of *TSC1* mutations correlated with response to treatment. This observation paves the way for future studies of whole-genome sequencing in an attempt to identify biomarkers of drug sensitivity in this disease.

The neoadjuvant setting as a paradigm for biomarker development

The traditional paradigm of oncologic drug development often involves first evaluating the efficacy of novel drugs in patients with advanced refractory disease. However, this may not be the optimal setting to detect a signal of drug activity and does not permit access to pre- and post-treatment tissue for biomarker development. Alternatively, the use of 'window of opportunity' trials, in which patients scheduled to undergo cystectomy receive a short course of treatment with a novel agent prior to surgery, allowing access to both pre- and post-treatment tissue, may be a more attractive setting for proof of concept and discovery studies. Furthermore, pathologic response rate to neoadjuvant therapy, an intermediate end point associated with improved outcomes in other solid tumors, may be utilized as a signal of activity in studies combining chemotherapy with a novel therapeutic.

Although neoadjuvant cytotoxic chemotherapy is standard for the treatment of muscle-invasive bladder cancer, treatment algorithms have been proposed to integrate 'window of opportunity' studies [43]. In one proposed approach, patients are stratified into low- and high-risk groups, distinguished by the presence of lymphovascular invasion, hydronephrosis, advanced clinical stage and variant histology. Patients with low-risk disease are offered enrollment in a single-agent neoadjuvant therapy. Pretreatment tissue (original diagnostic biopsy) and post-treatment tissue (radical cystectomy) are used for pharmacodynamic and molecular profiling. Patients with high-risk disease are offered enrollment in clinical trials that investigate the addition of a novel agent to conventional chemotherapy.

A few studies have recently been completed demonstrating the feasibility of this 'window of opportunity' approach. In one such study, 20 patients with muscle-invasive bladder cancer were treated with the EGF receptor inhibitor, erlotinib, 150 mg daily × 4 weeks followed by radical cystectomy [44]. In this trial, 25% achieved a pathologic complete response and 35% of patients were clinically downstaged. The Src inhibitor dasatinib has shown activity in Src-overexpressing human bladder cancer cell lines and the anti-tumor and biologic activity of dasatinib is currently being explored in a 'window of opportunity' neoadjuvant trial in patients with UC [45].

Conclusion

An improvement in our understanding of the underlying molecular pathogenesis has led to insights into the observed clinical heterogeneity of this disease. With the increased availability, and decreased cost, of high throughput genomic and proteomic technologies, such heterogeneity may be uncovered in much greater detail and ultimately linked to clinical outcomes. Such advances may not only facilitate more rational use of existing therapeutics, but also lead to the discovery of the next generation of treatments for this disease.

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Expert commentary

Current therapies for advanced urothelial carcinoma are limited by heterogeneity in outcomes and short response durations. Improved understanding of disease pathogenesis has led to investigation of altered proteins and pathways, both as biomarkers and therapeutic targets. Despite early promise, outcomes with 'targeted' therapeutics in unselected patients with advanced urothelial carcinoma have been disappointing. Continued identification and validation of relevant molecular pathway aberrations, and utilizing these biomarkers to select patients for appropriate therapies, are critical to delivering on the promise of personalized medicine for patients with advanced urothelial carcinoma.

Five-year view

Urothelial carcinoma is heterogeneous in terms of molecular pathogenesis, prognosis and response to antineoplastic agents. Significant progress has been made over the past decade in defining the common molecular aberrations in this disease, particularly with regards to potentially druggable pathways. However, translating these findings into clinically useful predictive biomarkers requires rigorous analytic and clinical validation, which has not routinely occurred with biomarker development. The next 5 years will likely markedly expand our knowledge of the molecular aberrations in individual tumors, with technologies such as next-generation sequencing, and lead to the first examples of truly personalized treatment for advanced urothelial carcinoma.

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Key issues

- Current therapies for advanced urothelial carcinoma are limited by extreme heterogeneity in patient outcomes and responses to treatment, thus necessitating the need for a more personalized approach to maximize clinical benefit.
- Identification of altered genes and pathways in high-grade urothelial carcinoma (e.g., *TP53* and *RB* genes) has provided further understanding of underlying pathogenesis, and also permits rational approaches to drug development, targeting the relevant pathways in given individuals.
- Use of biomarkers offers the promise of capturing disease heterogeneity not sufficiently captured with routine clinical and pathologic variables alone.
- A limited number of targets implicated in the pathogenesis of urothelial carcinoma, such as Her2-Neu and FGFR3, have already been explored in advanced urothelial carcinoma in molecularly defined patient populations.
- The neoadjuvant setting offers a unique paradigm for drug development, with pre- and post-treatment tissue available, ‘window of activity’ for pharmacodynamic and molecular profiling.

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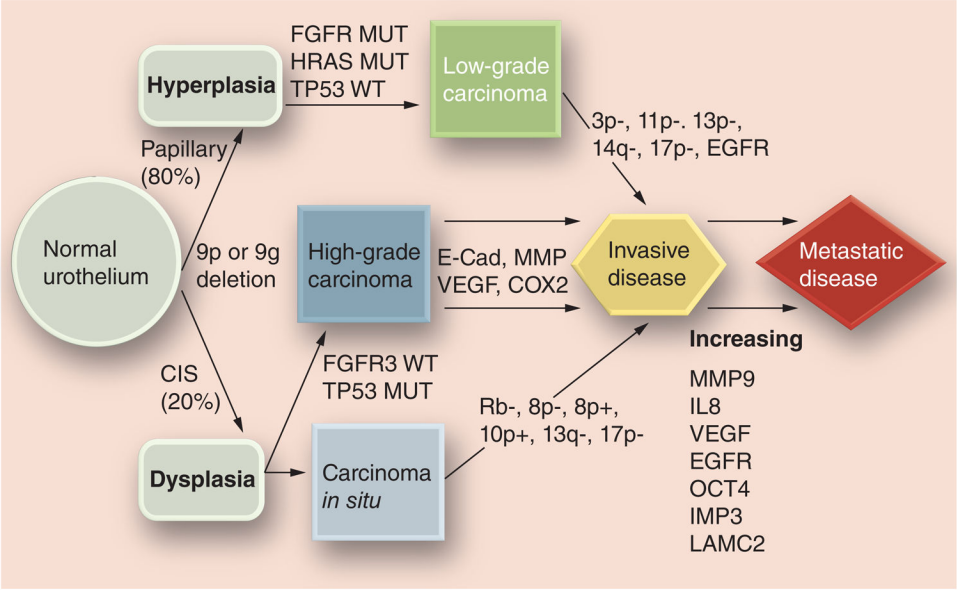

Figure 1. Molecular pathways in the progression of urothelial carcinoma

CIS: Carcinoma *in situ*; EGFR: EGF receptor; FGFR: FGF receptor; MUT: Mutation; WT: Wild-type.

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Table 1

Most common somatic mutations identified in urothelial carcinoma.

Somatic mutation	Frequency	Mechanism of action
FGFR3	40%	FGFR3 binds FGF, with downstream signaling leading to mitogenesis and differentiation
TP53	30%	Tumor suppressor gene; protein product can activate DNA repair, initiate apoptosis and cause cell growth arrest upon recognizing DNA damage
RB1	29%	Tumor suppressor gene; prevents the cell from replicating damaged DNA by preventing its progression along the cell cycle through G into S phase
PIK3CA	20%	Encoding the P110a protein, *PIK3CA* is mutated in several human cancers and believed to be oncogenic
CDKN2A	16%	Also known as *p16* gene, it encodes the multiple tumor suppressor-1 protein, which functions as a stabilizer of *p53* and sequester MDM-2
RAS (*HRAS*, *NRAS*, *KRAS*)	13%	As proto-oncogenes in the *RAS* family, even a single nucleotide change can lead to activating mutations in many tumor types.

FGFR3: FGF receptor 3.

Data taken from [102].