P53 Dysfunction in Colorectal Cancer

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Colorectal cancer (CRC) is one of the most common and fatal cancers worldwide. The carcinogenesis of CRC is based on a stepwise accumulation of mutations, leading either to an activation of oncogenes or a deactivation of suppressor genes. The loss of genetic stability triggers activation of proto-oncogenes (e.g., KRAS) and inactivation of tumor suppression genes, namely TP53 and APC, which together drive the transition from adenoma to adenocarcinoma. On the one hand, p53 mutations confer resistance to classical chemotherapy but, on the other hand, they open the door for immunotherapy, as p53-mutated tumors are rich in neoantigens. Aberrant function of the TP53 gene product, p53, also affects stromal and non-stromal cells in the tumor microenvironment. Cancer-associated fibroblasts together with other immunosuppressive cells become valuable assets for the tumor by p53-mediated tumor signaling.

Keywords: colorectal cancer ; p53 ; systemic therapy ; immunotherapy ; tumor microenvironment (TME) ; cancer-associated fibroblasts ; signaling ; targeted therapy

1. Introduction

According to the latest global cancer data of the World Health Organization (WHO), the global cancer burden increased to 18.1 million new cases and 9.6 million cancer deaths in 2018 [1]. Despite Europe representing only 9% of the world population, it accounts for 23.4% of global cancer cases and 20.3% of cancer-associated deaths. Colorectal cancer (CRC) is one of the most common cancers in women and men, and accounts for 12.6% (242,000 deaths) of cancer-related deaths in Europe [2]. In previous low-risk European countries such as Spain and several countries in eastern Europe, incidences have rapidly increased, which has been linked to dietary changes in relation to western lifestyle with a high calorie diet, rich in animal-derived proteins, especially red and processed meat, wheat products and high sugar consumption, combined with poor physical activity. Beside Europe, the regions of highest incidence of CRC are Australia and New Zealand, while in Japan, South Korea, countries in the middle east and Slovakia, CRC is the most diagnosed cancer among men [3]. Interestingly, all regions of Africa, as well as Southern Asia, have the lowest incidence rates for both cancers between both sexes [3][4]. But there seems to be a link, between incidence rates of CRC and increasing HDI (Human Development Index) in countries undergoing a major developmental transition [3][4].

In addition to diet and poor physical activity, other risk factors are family history of CRC (stronger association for first-degree relatives), inflammatory bowel disease, smoking, excessive alcohol consumption, obesity, and diabetes [5][6][7][8][9][10][11]. On the other hand, established protective factors are physical activity, the use of hormone replacement therapy, aspirin and, to a minor extent, diets rich in fruit, vegetables, cereal fiber and whole grains, dairy products, or fish and statin therapy. However, the most important preventative factor represents routine endoscopic check-ups, namely colonoscopy, with the extraction of precancerous lesions (polypectomy) [12][13][14][15][16][17][18][19].

CRC begins as a benign adenomatous intestinal polyp from epithelial tissue of the colon, which progresses to advanced adenoma with high-grade dysplasia, invasive adenocarcinoma and, ultimately, metastasis to distant organs such as the liver. This stepwise process is also known as a multistep tumorigenesis, with each step thought to be associated with specific genetic alterations in tumor suppressor genes or oncogenes [20][21].

There are distinct mutation patterns in CRC, which also impact disease progression and overall survival (OS). Mutations of the DNA mismatch repair system are frequently observed together with changes to oncogenes and/or tumor suppressor genes such as *KRAS*, *APC*, *PIK3CA* and *TP53* [22]. Among these, *TP53* is a central player as mutations of the encoded p53 protein are found in ~60% of CRCs, with only *APC* mutations (~80%) occurring more frequently [20][23]. Either loss- or gain-of-function (LOF/GOF) mutations of p53 drive tumor development and growth. LOF suspends the tumor-suppressing role of p53, whereas missense-type mutations tend to be associated with GOF, leading to acquisition of oncogenic properties [20]. In this context, p53 mutations may confer resistance to systemic therapy, which has a profound impact on treatment response and outcomes of patients. Understanding the role of p53 and its underlying mechanisms in CRC has significant implications for individualized and other emerging therapies. In this review, we address the role of p53

mutations for tumor cells as well as the tumor microenvironment and present implications for systemic treatments, immunotherapy and p53 targeting therapies in CRC.

1.1. The Physiological Role of p53 in CRC

Up to 60% of patients with CRC show somatic mutations of *TP53*, which is associated with poorer clinical outcomes [24]. *TP53* is also called “the guardian one of the genome” as it plays a crucial role for the regulation of the cell cycle and the stability of the genome. It represents one of the best characterized tumor suppressor genes and is located on the short arm of chromosome 17 (17p13.1). The encoded p53 protein consists of 393 amino acids with four functional domains. The centrally located sequence-specific DNA-binding domain (DBD) (amino acid position 101–306) allows binding to DNA and is frequently altered in p53 mutants, hindering its physiological function [25][26].

The p53 protein is rapidly degraded with a half-life of 6–20 min, with the amount of protein in cells primarily determined by its degradation. Under physiological conditions, p53 is degraded by the ubiquitin-mediated proteolysis. The E3 ubiquitin-protein ligase Mdm2 (MDM2) protein is one of the central enzymes to label p53 with ubiquitin, maintaining low expression of p53 under physiological conditions [26][27]. Under cellular stress, *TP53* becomes activated and p53 is overexpressed to induce cell cycle arrest, apoptosis and senescence. The p53 protein activates p21 (WAF1), a member of the cyclin-dependent kinase (CDK) inhibitors, which are involved in the inhibition of transition from G1 to S phase [28]. Direct activation of the Bcl-2 protein, Noxa and PUMA by p53 induces apoptosis. Further, p53 activates caspase-8 pathways through the activation of cell death receptors (e.g., Fas, DR5 or PIDD) [29]. Cellular senescence, where the cell is, for example, unable to divide, is induced by p53-mediated activation of p16, PML and p21 [30]. Moreover, p53 contributes to genome stability and the regulation of cell metabolism by minimizing mutagenic reactive oxygen species (ROS) [31][32]. Besides direct implications for cells, p53 also affects the surrounding microenvironment, controlling angiogenesis, cell migration and invasion, which will be discussed in detail later.

1.2. p53 Mutations in CRC

p53 mutations play a critical role in the adenoma–carcinoma transition during tumorigenesis [28][33]. Although it is mechanistically not fully understood, p53 mutations are less frequent in proximal colon tumors (34%), than in distal colorectal tumors (45%) [34]. The genetic mechanisms of *TP53* mutations include frameshift mutations caused by indels (insertions and deletions) or missense mutations, while the last occur more frequently in CRC [35]. In both cases, the outcome is either suppression of tumor suppressor activity due to LOF or GOF, promoting tumor development and growth [26]. p53 mutants retain their ability to form a protein-tetramer, which may therefore be a mixture of mutated and wild-type (wt-) p53 proteins [36]. In such complexes, wt-p53 protein is hindered from binding to its DNA binding site to express tumor suppressive transcripts due to LOF. GOF occurs when p53 mutants promote the expression of oncogenic transcripts. Here, p53 mutants together with transcription factors enhance the expression of tumor promoting transcripts [26][37].

In conclusion, although p53 alterations are based on distinct mutations, they lead to LOF or GOF of p53, which are hallmark events in the multistep tumorigenesis of CRC.

1.3. Treatment of CRC

Initiation of treatment is dependent on specific stratification and staging of the tumor by means of TNM and Union for International Cancer Control (UICC) classification systems. In general, CRC can be divided into four different clinical stages (based on UICC I to IV) according to the expansion of the tumor (T), lymph node (N) involvement and peripheral metastases (M). In this regard, it needs to be determined if the tumor is surgically resectable, if patients may benefit from a neo-/adjuvant chemotherapy, chemoradiotherapy (only rectal cancer) or, in the case of an advanced stage, if palliative chemotherapy needs to be initiated. In general, UICC stage I to III represents localized CRC and patients may undergo surgical resection. In stage II and III, adjuvant chemotherapy may be additionally applied in colon cancer [38]. In terms of rectal cancer, either neoadjuvant or adjuvant chemoradiotherapy in addition to surgical resection is initiated [39]. Stage II colon cancer is additionally stratified according to the microsatellite phenotype which aids in treatment decisions. In this context, a microsatellite stable (MSS) phenotype in comparison to high microsatellite instability (MSI-H) has been associated with a worse prognosis and therefore adjuvant chemotherapy is recommended in these patients [40]. Stage IV marks an advanced stage with distant metastases, also termed metastatic CRC (mCRC). In this case, palliative systemic therapy or resection of metastases is necessary. In mCRC, treatment decisions are also based on certain molecular signatures (wildtype or mutated (K)RAS and (B)RAF mutations) and on tumor site (left- or right-sided tumor) [41]. For a more detailed and in-depth discussion on CRC therapy, we refer to current practice guidelines [39][41]. How p53 can affect treatment response to systemic therapy during different clinical stages will be discussed in the following chapters.

2. The Impact of p53 on Treatment Outcomes of Colorectal Liver Metastasis (CRLM)

Approximately 25% of patients with CRC present with metastatic disease at the time of diagnosis [42]. The majority of these patients usually have colorectal liver metastasis (CRLM), as CRC is known to predominantly metastasize to the liver [43]. In the context of CRLM, *TP53* is also one of the most frequently mutated genes, and a predictor of a shorter OS [44]. Hepatic resection is considered the treatment of choice with five-year survival rates between 35% to 60% [45]. The introduction of effective downsizing regimens with chemotherapy has increased the eligibility of patients for resection [46], and showed an improvement in PFS [47]. However tumor recurrence within 12 months after liver surgery remains high [48]. Specifically *KRAS*- and *BRAF*-wt status have been identified as beneficial prognostic biomarkers regardless of the systemic therapy applied in addition to hepatic resection [49]. In a more recent analysis, concomitant mutations of *RAS* and *TP53* were associated with significantly lower five-year OS in comparison to wt-*TP53* among patients undergoing CRLM resection [50]. On the contrary, earlier studies suggested no impact of p53 mutations on long-term outcomes [49]. Instead of systemic therapy, hepatic arterial infusion (HAI) therapy, a locoregional high-dose liver-directed chemotherapy, can also be applied for patients with initially unresectable liver metastases. In this regard, HAI is applied during surgical laparotomy with an insertion of a catheter into the gastroduodenal artery, which remains the gold standard to date [51]. Although HAI has been associated with improved survival [52], patients with CRLM harboring p53 mutations were more resistant to hepatic arterial chemotherapy with floxuridine (fluorinated pyrimidine) [53]. In this context, patients with a high expression of p53 had a survival benefit [54] and a better treatment response [55], especially after 5-FU treatment via HAI. Moreover, in a comparison of patients with resectable and unresectable liver metastases receiving HAI and systemic therapy, concurrent *RAS*/*RAF* and *TP53* alterations were associated with worse survival in primarily unresectable patients [56]. Despite the administration of chemotherapy, adenoviruses containing a p53 transgene have also been developed and tested in phase I and phase II clinical trials for the treatment of p53-deficient cancers [57]. The HAI administration of such adenoviruses resulted in a higher nuclear p53 protein expression and increased apoptotic pathways in the tissues of CRLM [58]. However, following clinical trials of this approach are still lacking.

3. The Role of p53 in the Tumor Microenvironment

The tumor microenvironment (TME) increasingly gains the attention of oncologists as it hosts a plethora of immunosuppressive cells, which promote tumor growth and metastasis and counteract immunotherapy. Here, p53 plays a pivotal role not only in tumor cells but also in (non-)stromal cells of the TME (Figure 1) [59]. p53 was found to control tumor immune cell crosstalk as the inhibition of p53 degradation by the MDM2 inhibitor HDM201 increased CD8+ T cells and the CD8/Treg (regulatory T cell) ratio, leading to an improved immune mediated anti-tumor response [60]. The combination of HDM201 with PD-(L)1 blockade further increased the number of complete tumor regressions in a murine tumor xenograft model, suggesting that inhibition of p53 degradation or restoration of p53 might represent an appealing approach for cancer treatment. Besides an immunomodulatory function, p53 mutations dictate the composition of the tumor secretome, which consists of extracellular matrix (ECM) components, remodeling enzymes, exosomes and soluble mediators like growth factors, cytokines and chemokines (Figure 2). Stromal cells are corrupted by these signals and give rise to cancer-associated fibroblasts (CAFs), which are strong allies of the tumor in the TME [61][62][63][64][65][66]. They are the most abundant cell type of the TME and promote multiple aspects of tumor development and growth by three mechanisms: firstly, they remodel the ECM to increase its stiffness and thus inhibit immune cells from infiltrating the tumor stroma [67]; secondly, CAFs stimulate neo-angiogenesis via pro-angiogenic factors (e.g., ang1, 2; angiopoietin 1 and 2), securing the supply of oxygen and nutrients to the tumor [68]; and thirdly, together with tolerogenic cells of the adaptive and inherent immune system, CAFs sustain an immunosuppressive TME, also antagonizing the anti-tumor effect of checkpoint inhibitors [68][69][70][71][72][73]. Although CAFs derive from a variety of cell types, they can arise as a specific phenotype of activated myofibroblasts, which were instrumentalized by tumor mediated signals [68]. Mirroring their mesenchymal heritage, CAFs highly express α-smooth muscle actin (α-SMA), fibroblast activation protein (FAP), type I collagen, platelet derived growth factor receptor-alpha/beta (PDGFRα/β), vimentin, and the cell cycle regulating protein FSP-1 (fibroblast-specific protein, S100A4), which could be exploited for cell-specific drug targeting in the context of anti-stromal therapy [69]. There is rising evidence that the inhibition of p53 in stromal cells, including CAFs, causes immune escape and sustains tumorigenesis [61][74]. p53 is inhibited in stromal cells by onco-miRNA-30d, which is expressed in primarily hypoxic cells in the TME due to tumor triggered hypoxia (Figure 1) [75]. Thus, tumor cells can ablate wt-p53 function in the TME by a non-cell autonomous mechanism. In contrast, cancer cells are not affected by miRNA-mediated p53 inhibition because miRNA-30d only has negligible effects on mutated p53, putatively due to its high stability [76][77].

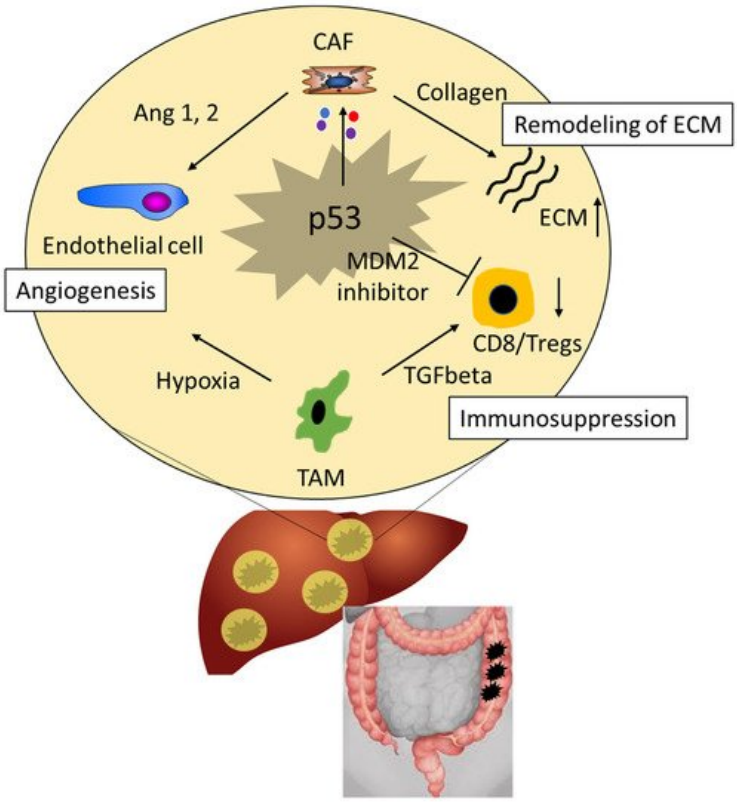

Figure 1. The role of p53 in the tumor microenvironment (TME) of CRC. p53 in tumor cells and surrounding (non-)stromal cells contributes to immune surveillance, angiogenesis and remodeling of extra-cellular matrix (ECM) in CRC. Ang 1, 2, Angiopoietin 1, 2; CAFs, cancer-associated fibroblasts; ECM, extra-cellular matrix; MDM2, E3 ubiquitin-protein ligase Mdm2; TAMs, tumor-associated macrophages; TGF-ß, transforming growth factor beta; Tregs, regulatory T cells.

Besides CAFs, tumor-associated macrophages (TAMs), as myeloid derived suppressor cells, contribute to an immunosuppressive microenvironment and support tumor growth as they are a source of immunosuppressive cytokines (e.g., CCL17, CCL18 and CCL22) and tumor promoting growth factors (VEGF-A, TNF-α) [68][78][79][80]. They stimulate the shift of anti-tumor CD8+ T cells towards immunosuppressive regulatory T cells, which favors immune tolerance and thus act as tumor-promoting agents [81]. In CRC, TAMs possess an intricate role, as their distribution towards the tumor might increase or hinder tumor growth [78]. High numbers of CD68+ TAMs in the invasive front were associated with favorable outcome, while other reports indicated that intratumoral CD68+ TAM counts were related with tumor penetration, lymph node metastasis and advanced stages of colorectal cancer [82][83][84]. Thus, the role of TAMs and their subsets remain to be defined. However, p53 was found to regulate cells of the innate immune system including TAMs. Although the underlying mechanism is unclear and needs further investigation, p53 expression in tumor cells correlated with CD204+ TAMs and density of tumor vessels in CRC [82].

Taken together, there is rising evidence that p53 in stromal and non-stromal cells contributes to immune surveillance of CRC in the TME and aberrant function of p53 promotes tumor growth.

4. p53 as a Druggable Target

The therapeutic targeting of mutated p53 is a promising concept in the treatment of CRC and proved to be effective in preclinical models. Therefore, pharmaceutical companies pursued two strategies: Firstly, they sought to develop small molecule inhibitors to directly address p53 mutants and, secondly, they aimed to target pathways which are corrupted by p53 mutants.

Restoration of wt-p53 can be achieved by cysteine-binding compounds (e.g., CP-31398, PRIMA-1, APR-246) [85][86]. Nascent mutant p53 can be refolded by these compounds to its wt-conformation. APR-246, a methylated analogue of PRIMA-1, binds to the p53 core domain, primarily via cysteine mediated binding, and enhances the thermostability of mutated p53, which promotes refolding of mutated p53 to p53 wt-conformation [86][87]. APR-246 is tested in several phase II clinical trials together with carboplatin combination chemotherapy in patients with serous ovarian cancer with mutated p53 (NCT02098343), a combination of APR-246 with azacytidine in p53 mutant myeloid neoplasms (NCT03072043) and a combination of APR-246 with 5-FU and cisplatin in esophageal cancer (NCT02999893) [88].

Besides cysteine-binding compounds, small molecule drugs, such as PK083 and PK7088, bind specifically to the surface cavity of the Y220C p53 mutant and induce refolding to p53 wt-conformation [89][90].

Proper folding of wt-p53 requires zinc as a cofactor, while mutants have a lower affinity to bind zinc. The addition of zinc to cells has been shown to restore the ability of p53 mutants to bind zinc, preventing tumor progression [91]. In this vein, the zinc metallochaperone-1 (ZMC-1), also named as NSC319726, was discovered by screening of the NCI-60 tumor cell line panel and was found to restore the proper folding and transcriptional activity of p53 mutants [91]. ZMC-1 has been shown to induce apoptosis in murine tumor cells of xenograft models, which carry the specific p53 mutation R172H; a mutation, which also exists in human tumors, designated as R175H [92]. In addition, COTI-2, another Zn2+-chelating compound, restores the folding and function of p53 mutants, inhibiting the PI3K–AKT pathway. This leads to tumor cell death and prevents tumor growth in murine xenografts. While the exact mechanism is still under investigation, COTI-2 has already been tested for gynecological and head and neck cancers in phase I clinical trials [26][93]. Furthermore, the small molecule drug, P53R3, has been shown to restore the DNA-binding ability of specific p53 mutants such as 175H, R273H and M237 [94].

While most of the investigational drugs seek to stabilize the wild-type conformation of p53 or enhance the binding to the DNA target site, SCH529074 binds to the p53 mutant's core domain and increases p53 target gene expression. Additionally, SCH529074 inhibits degradation of p53 by reducing MDM2 mediated p53 ubiquitination [95].

Beside restoring the function and wt-conformation of p53 mutants, other therapeutic strategies seek to deplete or enhance the degradation of p53 mutants. Schulz-Heddergott et al. demonstrated that the heat shock protein (Hsp) inhibitor Hsp90 abrogates Jak2/Stat3 signaling in mouse CRC models by depletion of mutated p53 (R248Q allele), which suppressed tumor growth [96]. Ganetespib, another highly potent Hsp90 inhibitor, was tested in a clinical trial for non-small lung cancer but the drug was found to be futile when compared with standard regimes and the trial was stopped after the first interim analysis [97]. Furthermore, the histone deacetylase (HDAC) inhibitor SAHA degrades mutated p53 by inhibiting HDAC6 and disrupting the HDAC6-HSP90-p53 mutant axis, which is specifically activated in p53 mutants [98].

The repurposing of established drugs is an economically interesting concept that can help to reduce substantial costs in drug development and to bypass the slow pace of new drug discovery. Here, in the clinic already used and so de-risked compounds may be reproposed to treat diseases other than those they were originally approved for [99]. Statins are well known drugs with a favorable safety profile and are applied to treat patients with hypercholesterolemia disease. Statins reduce HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase, which is a central enzyme in lipid metabolism. In addition, HMG-CoA controls prenylation/lipidation of proteins. Prenylation is central for different cellular processes like adhesion, migration, and proliferation signaling [26]. p53 binds to sterol regulatory element-binding protein (SREBP) and leads to prenylation of oncogenic proteins in breast cancer [100]. Additionally, statins suppress the Rho GTPases' prenylation, which promotes nuclear localization and activation of the YAP/TAZ in tumor development [101]. Thus, statins can interrupt these mechanisms, leading to an anti-tumor effect in breast cancers.

Another appealing concept is the use of small interfering RNA (siRNA) to deplete p53 mutants, especially for liver metastasis. The use of siRNA allows for the therapeutic knockdown of virtually any gene (also specific p53 mutants) without affecting other non-targeted genes. Since siRNA offers poor pharmacokinetics and stability in the blood stream, nanoparticles are the ideal vehicles to transport siRNA to liver. We have developed nanohydrogel particles as siRNA carriers, which are therapeutic gene knockdown in liver fibrotic mice [102][103]. Surface modified nanocarriers with target cell specific ligands can also be applied to cell-specific siRNA delivery to cancer cells. Therefore, nanohydrogel particles were coated with mannose for cell-specific siRNA delivery to hepatic M2 polarized macrophages, sharing characteristics of TAM [104][105].

Recently, Han-Chung Hsiue E. et al. published an interesting study where the most common *TP53* mutant R175H (in which arginine at position 175 is replaced with histidine) was targeted with a bispecific antibody (H2) [106]. The highly specific antibody binds to human leukocyte antigen-A (HLA-A) allele on the cell surface, which presents peptide fragments of the $TP53^{R175H}$ mutant, while its other domain binds to a T-cell receptor to trigger an antitumor response. The bispecific antibody proved to be effective in preclinical models and induced regression of human xenograft tumors in mice, both in early and established tumors.

In summary, there are promising drug candidates for targeting p53 mutants in CRC under development, while only a few drugs are already tested in clinical trials or have shown therapeutical benefit in the clinic. One of the major hurdles is that there is no drug to target all p53 mutants. In the context of personalized medicine, the specific p53 mutations of each

patient differs, hence there is need for personalized assessment in order to choose the appropriate combinatorial regimes for targeting p53 mutants together with standard drugs to treat patients with CRC.

A list of relevant drugs targeting p53 mutants in CRC is shown in Table 1.

Table 1. List of drugs targeting p53 mutants in CRC.

	Drug	Type of Drug	Mechanism	Stage of Development	Reference
1.	APR-246	Small molecule	Restores wild-type conformation	Clinical phase II	[86][87][88]
	CP-31398	Small molecule	Restores wild-type conformation	Preclinical	[26][89]
2.	PK083	Small molecule	Restores wild-type conformation	Preclinical	[26][89]
3.	PK7088	Small molecule	Restores wild-type conformation	Preclinical	[26][93]
4.	Zinc	Cofactor	Restores wild-type conformation	Preclinical	[26]
5.	ZMC-1	Zn2+-chelating compounds	Restores wild-type conformation	Preclinical	[92]
6.	COTI-2	Zn2+-chelating compounds	Restores wild-type conformation	Clinical phase I	[93]
7.	P53R3	Small molecule	Restores DNA-binding ability	Preclinical	[26]
8.	SCH529074	Small molecule	Restores DNA-binding ability and prevents degradation of p53	Preclinical	[95]
9.	Hsp90 inhibitor	Small molecule	Depletion of p53 mutants	Preclinical	[96]
10.	Ganetespib (potent Hsp90 inhibitor)	Small molecule	Depletion of p53 mutants	Discontinuation of clinical phase I	[97]
	SAHA	Small molecule	Depletion of p53 mutants	Preclinical	[98]
11.	Statins	Small molecule	Inhibition of p53 mutant related downstream targets	Preclinical	[100][101]
12.	siRNA	RNA based therapy	Specific knockdown of p53 mutants	No data yet available	
13.	H2	Bispecific antibody	Specific targeting of *TP53*^{R175H}	Preclinical	[106]

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