

Rescuing the Guardian of the Genome: A Brief Commentary on Rezatapopt, a p53^{Y220C}-Reactivating Therapy

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ABSTRACT

The loss of function of tumour protein 53 (p53) is a critical event in the genesis, progression, and therapy-resistance of many cancers. *TP53*, the gene which encodes p53, is estimated to be mutated in at least 50% of all malignancies. Due to its homotetrameric structure, p53 is vulnerable to dominant negative mutations, whereby even heterozygosity of *TP53* can promote oncogenesis. Given the role of p53 and frequency at which *TP53* mutations are detected in cancer, restoring p53 function has been investigated as a basis for targeted antineoplastic therapy. In this brief commentary, the current state of rezatapopt (PC14586)-a p53^{Y220C}-reactivating therapy-is summarized.

Keywords: p53-reactivating therapy; oncology; rezatapopt; *TP53*; Y220C

Background

The tumor protein 53 (p53) is a key tumor suppressor inactivated in well over 50% of all cancers¹. Mutations in *TP53*, the gene encoding p53, are common events in the genesis, progression, and treatment-resistance of virtually all cancer types. Notably, as a homotetramer, p53 is vulnerable to dominant-negative (DN) mutations; thus, even heterozygosity of *TP53* with a DN mutation is oncogenic, as the remaining wild-type p53 subunits are antagonized². Given the importance of p53 in preventing cancer and the frequency at which *TP53* is mutated in cancer, the restoration of p53 function has been investigated as a mechanism for targeted antineoplastic therapy^{3,4}.

As the p53 protein is actively regulated by the ubiquitin-

proteasome system and nuclear import/export, there are many points at which p53 homeostasis can plausibly be targeted to increase intracellular/intranuclear levels³. Regarding *TP53* itself, broadly, pathogenic mutations impair either the DNA-binding or oligomerization abilities of p53. As such, many p53-reactivating therapies (p53RT) have focused on correcting the structure of mutant p53, forcing the misshapen protein into the wild-type conformation, thereby restoring its tumor-suppressive function. The Y220C mutation is a *TP53*-inactivating mutation that causes the production of a thermally unstable, non-functional protein^{3,5}. However, the Y220C mutation simultaneously creates a hydrophobic “pocket” in p53, imparting a vulnerability to certain small molecules, such as rezatapopt (PC14586 [REZ]; PMV Pharmaceuticals, Inc., Princeton, NJ, USA; **Figure 1**)⁵⁻⁷.

REZ is a first-in-class p53RT that binds within the hydrophobic pocket of p53^{Y220C}, thereby stabilizing the Y220C-mutated protein, effectively restoring its tumor-suppressive activity.

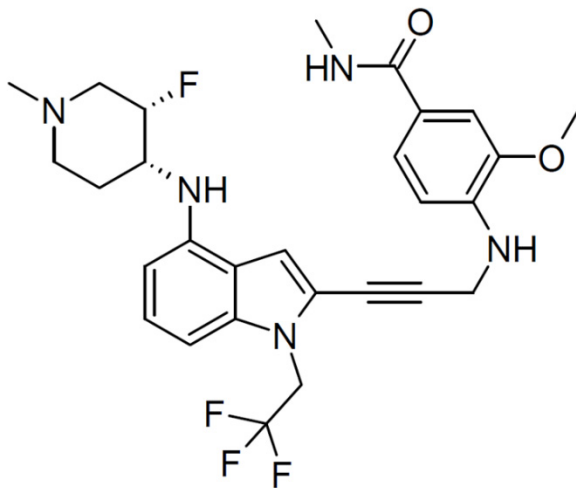


Figure 1: Chemical structure of rezatapopt (Wikimedia Commons [public domain]).

Recent Trials

In the PYNACLE phase I trial (NCT04585750) of patients with locally advanced or metastatic *TP53*^{Y220C}-mutated solid tumors who were heavily pretreated (n = 77), REZ was largely well-tolerated, with nausea and vomiting as the most common side effects⁷. Nearly all patients (99%) had at least one adverse event (AE), and 38% had a grade 1 or 2 AE. Of grade 3 and 4 AEs, anemia was the most common, occurring in 14% and 1% of patients, respectively, and 36% of patients total. Anemia was the only grade 4 AE to occur, and no grade 5 AEs occurred. In terms of secondary (outcome-related) endpoints, 71 patients had measurable disease at baseline and were eligible for assessment. Overall response assessed by investigator and blinded independent central review was 20% for both. Half of responding patients had ovarian cancer. The median time to response was 1.4 months, and median duration of response was 7.0 months. The median progression-free survival was 4.3 months, and median overall survival was 11.4 months. Notably, all responding patients (20%) had wild-type KRAS and no patients harboring a KRAS mutation (29%) demonstrated a response.

Most currently, REZ is being studied in combination with azacitidine with or without venetoclax in a phase Ib trial (NCT06616636) of patients with *TP53*^{Y220C}-mutated acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS)⁸. The trial's primary endpoint is to assess the safety/tolerability of REZ. Secondary endpoints are: 1) determining the efficacy of REZ in relapsed/refractory and newly diagnosed patients with *TP53*^{Y220C}-mutated AML/MDS; 2) assessing event-free survival and overall survival in patients receiving REZ in combination with azacitidine (AZA) with or without venetoclax; 3) assessing duration of response in patients receiving REZ in combination with AZA; 4) characterizing the pharmacokinetics of REZ in combination with AZA. Exploratory objectives are: 1) assessing changes in the variant allele frequencies of *TP53*^{Y220C} mutations via next-generation sequencing; 2) describing the mutation profiles of patients at screening, response, and relapse, and correlating to clinical parameters; 3) assessing changes in

clonal architecture based on bone marrow aspirates via single-cell sequencing; 4) evaluating for p53 activation and changes in the immunologic profile of patients.

Commentary

REZ appears to be mostly well-tolerated and has shown some preliminary antineoplastic activity as monotherapy in *TP53*^{Y220C}- but not KRAS-mutated solid tumors, particularly ovarian cancer. The efficacy of REZ does seem to be limited by co-occurring KRAS mutations, which are very common in many types of cancer, including AML and MDS^{9,10}. Accordingly, co-investigation with KRAS blockade would be of interest.

As with any therapy-targeted or conventional-resistance to REZ remains a concern. In fact, several secondary resistance mutations have already been detected in REZ-treated patients, illustrating the importance of p53 inactivation in oncogenesis¹¹. As is the case with virtually all antineoplastic treatment regimens, a multi-modal, non-overlapping approach will likely be required for the durable efficacy of REZ in both treatment-naïve and -experienced patients.

REZ represents an early albeit intriguing candidate as a potential novel, targeted therapy for *TP53*^{Y220C}-mutated malignancies.

Ethics approval

Not applicable.

Conflicts of interest

None.

Funding

None.

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