ISSN: 2584-0355
DOI: doi.org/10.51219/MCCRJ/Austin-P-Runde/536

URF PUBLISHERS
connect with research world

Medical & Clinical Case Reports Journal

https://urfpublishers.com/journal/case-reports

Vol: 4 & Iss: 4

Commentary

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

Austin P. Runde, MS*

MD Program, Stritch School of Medicine, Loyola University Chicago, Maywood, IL, USA

Citation: Runde AP. Rescuing the Guardian of the Genome: A Brief Commentary on Rezatapopt, a p53Y220C-Reactivating Therapy. *Medi Clin Case Rep J* 2026;4(4):2043-2045. DOI: doi.org/10.51219/MCCRJ/Austin-P-Runde/536

Received: 15 October, 2026; **Accepted:** 16 October, 2026; **Published:** 19 October, 2026

***Corresponding author:** Austin P. Runde, MS, MD Program, Stritch School of Medicine, Loyola University Chicago, Maywood, IL, USA

Copyright: © 2026 Runde AP., This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

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 cancers[1]. 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 antagonized[2]. 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-proteosome system and nuclear import/export, there are many points at which p53 homeostasis can plausibly be targeted to increase intracellular/intranuclear levels[3]. 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.

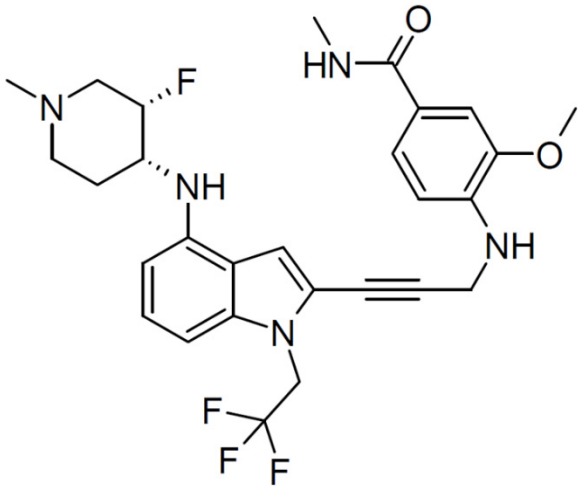


Figure 1: Chemical structure of rezatapopt (Wikimedia Commons [public domain]).

Recent Trials

In the PYNNACLE 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 effects[7]. 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 oncogenesis[11]. 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.

References

1. Lozano G. Restoring p53 in cancer: the promises and the challenges. J Mol Cell Biol 2019;11(7):615-619.
2. Gencel-Augusto J, Lozano G. p53 tetramerization: at the center of the dominant-negative effect of mutant p53. Genes Dev 2020;34(17-18):1128-1146.
3. Wang W, Liu X, Liu H, et al. p53: from understanding its structure to advances in therapeutic targeting. Signal Transduct Target Ther 2026;11(1).
4. Bossi G, Sacchi A. Restoration of wild-type p53 function in human cancer: relevance for tumor therapy. Head Neck 2007;29(3):272-284.
5. Vu BT, Dominique R, Fahr BJ, et al. Discovery of Rezatapopt (PC14586), a First-in-Class, Small-Molecule Reactivator of p53 Y220C Mutant in Development. ACS Med Chem Lett 2025;16(1):34-39.
6. Ma Z, Shen Q, Zhou J. Rezatapopt (PC14586): A First-in-Class Small Molecule p53 Y220C Mutant Protein Stabilizer in Clinical Trials. J Med Chem 2025;68(7):6847-6849.
7. Dumbrava EE, Shapiro GI, Parikh AR, et al. Phase 1 Study of Rezatapopt, a p53 Reactivator, in TP53 Y220C-Mutated Tumors. N Engl J Med 2026;394(9):872-883.
8. Lane DP. Confirmation by conformation: rescue of mutant p53 in AML. Blood 2025;146(21):2503-2504.
9. Zhang J, Wang J, Liu Y, et al. Oncogenic Kras-induced leukemogeneis: hematopoietic stem cells as the initial target and lineage-specific progenitors as the potential targets for final leukemic transformation. Blood 2009;113(6):1304-1314.

10. Zhang Y, Ma Y, Zhang K, et al. KRAS Mutations in Cancer: From Molecular Insights to Therapeutic Strategies. Am J Clin Oncol 2025;48(8):383-391.

11. Fece de la Cruz F, Varkaris A, Patel PS, et al. Acquired On-Target Alterations Drive Clinical Resistance to p53-Y220C Reactivators. Cancer Discov 2026;16(4):677-685.