A Report on "Phase 1 Study of Rezatapopt, a p53 Reactivator, in TP53 Y220C–Mutated Tumors" by Dumbrava et al. (2026)

Reviewer 2

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> I am wiser than this person; for it is likely that neither of us knows anything fine and good, but he thinks he knows something when he does not know it, whereas I, just as I do not know, do not think I know, either. I seem, then, to be wiser than him in this small way, at least: that what I do not know, I do not think I know, either.
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> Plato, *The Apology of Socrates*, 21d

> To err is human. All human knowledge is fallible and therefore uncertain. It follows that we must distinguish sharply between truth and certainty. That to err is human means not only that we must constantly struggle against error, but also that, even when we have taken the greatest care, we cannot be completely certain that we have not made a mistake.
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> Karl Popper, 'Knowledge and the Shaping of Reality'

Overview

Citation: Dumbrava, E.E., Shapiro, G.I., Parikh, A.R., Johnson, M.L., Tolcher, A.W., Thompson, J.A., El-Khoueiry, A.B., Vandross, A.L., Kummar, S., Shepard, D.R., LeDuke, K., Sheehan, L., Alland, L., Haque, A., Jalota, D., Fellous, M., and Schram, A.M. (2026). Phase 1 Study of Rezatapopt, a p53 Reactivator, in TP53 Y220C–Mutated Tumors. *New England Journal of Medicine*. Vol. 394, No. 9, pp. 872–883.

Abstract Summary: This phase 1 study evaluated rezatapopt, an oral, selective p53 reactivator, in heavily pretreated patients with locally advanced or metastatic solid tumors harboring a TP53 Y220C mutation. The study aimed to determine the maximum tolerated dose and recommended phase 2 dose, assessing dose-limiting toxic effects, adverse events, and preliminary efficacy.

Key Methodology: Phase 1, single-group, dose-escalation and dose-optimization study with 77 heavily pretreated patients. Endpoints included dose-limiting toxic effects, adverse events, efficacy, and pharmacokinetic features. Overall response was assessed by investigator and blinded independent central review.

Research Question: What are the maximum tolerated dose, recommended phase 2 dose, safety, tolerability, and preliminary efficacy of rezatapopt in patients with advanced solid tumors harboring a TP53 Y220C mutation?

Summary

Is It Credible?

Dumbrava et al. present the results of a phase 1 dose-escalation and dose-optimization study evaluating rezatapopt, a first-in-class targeted therapy designed to reactivate mutant p53 protein. The trial enrolled heavily pretreated patients with locally advanced or metastatic solid tumors harboring a specific mutation, TP53 Y220C. The authors claim to have successfully identified a maximum tolerated dose and selected a recommended phase 2 dose of 2000 mg once daily administered with food. They report that the drug has a manageable safety profile, primarily characterized by nausea and vomiting. Crucially, the authors claim that "Antitumor activity occurred across multiple tumor types, providing proof of concept for p53 reactivation" (p. 872). They highlight an overall response rate of 20% across all patients, which increased to 30% among a subgroup of patients who received a dose of at least 1150 mg once daily and had a KRAS wild-type tumor. Finally, they assert that observed reductions in circulating tumor DNA suggest "on-target activity of rezatapopt" (p. 879).

The headline efficacy claim of a 30% response rate requires careful interpretation, as it relies on a post-hoc definition of an "observed efficacious-dose range" of 1150 mg or higher. The study's statistical analysis plan originally specified that efficacy would be summarized by assigned dose level (SAP, p. 39). Grouping the higher doses together after observing where responses occurred is a common exploratory practice in early-phase trials, but utilizing this post-hoc grouping to calculate and highlight a specific response rate risks inflating the perceived efficacy of the drug. Furthermore, the clear dose-response relationship reported by the authors could potentially be confounded by baseline patient characteristics. Because the article does not provide a demographic or clinical breakdown by specific dose cohorts, it is difficult to

entirely rule out selection bias between the lower-dose and higher-dose groups.

The authors' conclusions regarding KRAS mutations also warrant a degree of epistemic humility. The abstract states definitively that all responding patients had wild-type KRAS, framing the mutation as a barrier to efficacy. However, the text acknowledges that nearly 60% of patients with a KRAS variant achieved stable disease. This suggests that rezatapopt likely retains some level of biological activity in these tumors, even if it does not induce objective tumor shrinkage. Framing KRAS mutations as an absolute resistance marker might be an over-interpretation of the preliminary data.

The article's assertion that the trial provides "proof of concept" for p53 reactivation is somewhat weakened by the omission of planned mechanistic data. The study protocol explicitly designated the measurement of p21 and MDM2 protein levels in tumor biopsies as direct "on-target biomarkers of PC14586 binding activity," as these are direct downstream targets of a functional p53 protein (Protocol, p. 101). The complete absence of these protein-level results from the article is a notable limitation. Instead, the authors rely on reductions in the TP53 Y220C variant allele frequency in circulating tumor DNA to demonstrate on-target activity. While informative, circulating tumor DNA data were only available for 41 of the 77 patients (53%), and the article does not explain this large proportion of missing data, leaving the analysis vulnerable to selection bias.

Finally, the rationale provided for the recommended phase 2 dose presents a complex safety trade-off that is not fully explored in the main text. The authors justify selecting the 2000 mg dose with food based on a lower incidence of gastrointestinal toxicities and higher drug exposure. However, supplementary data reveal that the rate of severe (grade 3 or 4) treatment-related adverse events was numerically higher in the fed cohort (33.3%) compared to the fasting cohort at the same dose (18.2%). While the sample sizes are small, the justification would be more robust if it directly addressed this trade-off. The article also omits preclinical data showing poor blood-

brain barrier penetration, which was the original protocol's rationale for excluding patients with primary central nervous system tumors from the Phase 1 trial.

Ultimately, the study successfully establishes a recommended phase 2 dose and provides genuinely new, preliminary evidence of antitumor activity for a novel therapeutic approach. However, the most prominent efficacy figures rely on post-hoc subgroupings, and the mechanistic claims are undermined by the absence of planned protein-level biomarker data and incomplete circulating tumor DNA reporting.

The Bottom Line

Dumbrava et al. provide valuable preliminary evidence that rezatapopt, a novel p53 reactivator, can induce tumor responses in heavily pretreated patients with TP53 Y220C mutations. However, the most impressive efficacy claims rely on a post-hoc definition of an efficacious dose range, which may inflate the perceived benefit. Furthermore, the study's assertion of mechanistic proof of concept is weakened by the omission of planned protein-level biomarker data and reliance on incomplete circulating tumor DNA analyses. Despite these limitations, the trial successfully establishes a recommended phase 2 dose and demonstrates sufficient clinical activity to warrant further investigation.

Potential Issues

Omission of planned mechanistic biomarker data: The article's evidence for the drug's proposed mechanism of action—the refolding and functional reactivation of the p53 protein—is weakened by the omission of direct biomarker analyses. The study protocol designated the measurement of p21 and MDM2 protein levels in tumor biopsies as "on-target biomarkers of PC14586 binding activity," as these proteins are direct downstream targets of reactivated p53 (Protocol, p. 101). However, the article does not report the results of these analyses. Instead, it relies on a less direct marker, the reduction of the *TP53 Y220C* variant allele frequency in circulating tumor DNA (ctDNA), to suggest "on-target activity" (p. 879). While a reduction in ctDNA indicates a response in the targeted tumor clone, it does not provide direct evidence of the specific molecular mechanism of p53 reactivation. The protocol specified that these tumor biopsies were optional (Protocol, p. 100), which may explain the absence of data if an insufficient number of paired samples were collected. Nonetheless, the failure to report results from the pre-specified, more direct mechanistic assays is a significant limitation.

Use of a post-hoc defined "efficacious-dose range" may inflate efficacy claims: The study defines an "observed efficacious-dose range" (doses ≥1150 mg) and reports its most favorable efficacy result—a 30% overall response rate—within a subgroup of patients treated in this range (p. 872). This dose range was not pre-specified in the study protocol or statistical analysis plan and appears to have been defined post-hoc based on the doses at which responses were observed. The statistical analysis plan specified that efficacy would be summarized by "dose level" (SAP, p. 39). While it is standard practice in early-phase trials to describe the dose range where activity was seen, using this post-hoc grouping to calculate and highlight a higher response rate for a specific subgroup can create an inflated perception of the drug's efficacy. The article is transparent in labeling the range as "observed" (p. 875), but the reliance on

this post-hoc definition for a key efficacy claim is a limitation.

Potentially incomplete justification for the recommended phase 2 dose: The article's rationale for selecting 2000 mg once daily with food as the Recommended Phase 2 Dose (RP2D) presents a complex safety and pharmacokinetic trade-off that is not fully explored. The text justifies the choice by citing a "lower incidence of gastrointestinal toxic effects" in the cohort that received the drug with food (p. 876). However, data in the Supplementary Appendix show that the rate of severe (Grade 3 or 4) treatment-related adverse events was higher in the chosen RP2D cohort (2000 mg with food: 33.3%, or 6 of 18 patients) compared to the same dose administered without food (18.2%, or 2 of 11 patients) (Table S3, p. 29). The article addresses this by stating that the incidence of these events was "similar across the cohorts" (p. 877), a characterization that is reasonable given the small sample sizes. The authors also provide a pharmacokinetic rationale, noting that administration with food "led to a higher level of drug exposure" and "lower level of within-patient variability" (p. 881). While these are valid reasons for dose selection, the justification would be more complete if it directly addressed the trade-off between improved gastrointestinal tolerance and the numerically higher rate of overall severe toxicities.

Potential over-interpretation of KRAS mutation status as a resistance marker: The article's conclusion that co-occurring *KRAS* mutations confer resistance to rezatapopt may be overstated. The abstract makes the strong factual claim that "All patients with a response had a solid tumor that harbored TP53 Y220C and wild-type KRAS" (p. 872). While this is a notable finding from a post-hoc subgroup analysis, the article's own data suggests a more complex picture. The discussion acknowledges that "nearly 60% of the patients with a KRAS single-nucleotide variant had stable disease" (p. 881), indicating that the drug retains some level of biological activity in this subgroup, even if it does not lead to objective tumor shrinkage. The article's narrative emphasizes the lack of objective responses, which may lead readers to interpret the finding as evidence of complete resistance, a conclusion that

is not fully supported when the high rate of disease stabilization is considered. The authors appropriately call for "further mechanistic studies" (p. 881), but the overall framing of the finding may be stronger than the data warrant.

Potential for confounding in the dose-response relationship: The article reports a clear dose-response relationship for efficacy, noting that "No patients treated with a dose that was lower than the observed efficacious-dose range [≥1150 mg] had a response" (p. 878). However, this conclusion is subject to potential confounding by differences in patient characteristics between the lower-dose and higher-dose cohorts, a common limitation in sequential dose-escalation studies. The article does not provide a breakdown of key prognostic factors—such as ECOG performance status or number of prior therapies—by dose cohort. Table 1 aggregates these characteristics for all 77 patients (p. 876). While the very small number of patients in the lowest dose cohorts (n=10 total across doses from 150 mg to 600 mg) would make a formal statistical comparison difficult, the absence of these data means that the possibility of confounding by patient selection cannot be ruled out.

Omission of preclinical data on poor brain penetration: The article fails to provide the scientific rationale for excluding patients with primary central nervous system (CNS) tumors from the trial. The original study protocol provides a specific and material reason: preclinical studies in rats showed that the drug's concentration in the brain was only 10% of that in the plasma (Protocol, p. 64). This finding suggests that the drug has poor penetration of the blood-brain barrier and is unlikely to be effective for brain tumors. By omitting this negative preclinical finding while noting the exclusion of patients with primary CNS tumors (p. 874), the article does not present important information about a known pharmacological limitation of the drug.

Minor presentation and transparency issues: Several minor issues related to data presentation and transparency are present. First, the analysis of circulating tumor DNA is based on data from only 41 of 77 patients (53%), and the article does not

explain why data is missing for the remaining 47% of the cohort, leaving the analysis open to potential selection bias (p. 879). Second, the reasons why 14% of the efficacy-evaluable population were "Not evaluated" for response are not specifically detailed, creating a small gap in the efficacy analysis (p. 878). Third, the article notes several unusual instances where the blinded independent central review upgraded investigator-assessed responses (e.g., from stable disease to partial response) but does not offer an explanation for this pattern (pp. 879, 881). Fourth, while the article clarifies that the 8 fatal adverse events were not treatment-related, it omits the specific causes of death, which are typically reported for completeness in a Phase 1 trial (p. 877). Finally, the abstract's summary of the safety profile is framed in a potentially confusing manner by highlighting the minority of patients (38%) whose most severe adverse event was low-grade, rather than directly stating the rate of high-grade events (p. 872).

Future Research

Direct mechanistic validation: Future research should prioritize the collection and reporting of paired pre-treatment and on-treatment tumor biopsies to directly measure downstream targets of p53 reactivation, such as p21 and MDM2 protein levels, to definitively establish the drug's mechanism of action in humans.

Pre-specified efficacy evaluations: Subsequent phase 2 and phase 3 trials must utilize strictly pre-specified dose cohorts and stratify efficacy outcomes by baseline patient characteristics to confirm the true response rate and rule out confounding variables that may have influenced the dose-response relationship observed in this early-phase study.

Clarification of resistance mechanisms: Further investigation is needed to explore the exact biological interaction between TP53 Y220C and co-occurring KRAS mutations, specifically to determine whether KRAS alterations entirely abrogate rezatapopt's efficacy or merely shift the clinical benefit from objective tumor shrinkage to prolonged disease stabilization.

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