WOLFPACK RESEARCH

PMV Pharma (PMVP) We Believe Next Week's Critical Phase I Data Will Disappoint

- PMV's preclinical laboratory results for their primary drug candidate appear to have been photoshopped, raising an initial red flag that PMV may have cherrypicked data to spin a positive story on lackluster results. (A consultant reached out to management to discuss these issues, but the company declined).

- There is compelling evidence that PMV Pharma's primary drug candidate will fail, and the Phase I data scheduled for release on May 26th [1] will disappoint. PC14586, an oral pill for the treatment of cancer, does not have a viable replacement candidate in the pipeline, which means PMV is significantly overpriced.

- PMV's preclinical tests on mice showed that its drug needs to be administered at much higher doses than other comparable drugs to achieve positive results, and higher dosing increases the risk that the drug's toxicity will outweigh any potential benefits.

- PMV's preclinical results also show that the drug has a brief therapeutic window and almost completely disappears after 24 hours. This is another red flag and indicates that PMV's drug lacks the potency needed to make it a viable candidate for FDA approval.

- PMV has not released their Phase I results yet, but management's early disclosures to select sell-side analysts indicate that PMV is trying to add subjects and up the dosage in their clinical trial to garner better results. This provides more evidence that PMV's primary drug candidate is not potent enough to act as a single-agent therapy (a must for FDA approval), without toxic side effects.

- PMV's lead drug reminds us of Aprea's eprenetapopt, a small molecule designed to reactivate p53 protein. Aprea's drug failed to show a statistically significant improvement in late 2020 and the stock cratered 77%.

- With their primary candidate dead, PMV's current assets will only consist of a broken pipeline and less than $300 million in cash, not worth their lofty $628 million valuation.

[1] The abstract for the Phase I trial is due to come out on May 26, 2022. Lackluster results may terminate PC14586.

Introduction: Understanding the p53 Protein

Mutations in the p53 Protein Are a Focus of Cancer Research Because Mutations in the Protein Allow for Cancer Cells to Survive and Spread

Known as the "guardian of the genome," the p53 protein detects cell mutations and initiates a process to repair damage at a molecular level or activates apoptosis (programmed cell death) if the repair is unsuccessful. Mutations in the p53 protein limit its ability and result in the survival and progression of cancer cells it would otherwise target.[2] P53 mutations are present in approximately 50-60% of all cancers and p53 has been a focus for cancer researchers since its discovery in 1979.

Decades of research have identified specific hotspots or point mutations in the gene. These point mutations occur when a single DNA base change from the wild-type (normal) p53 gene can inactivate the p53 protein and result in the survival and unchecked progression of cancer cells. Many human genes require multiple mutations to fail, but unfortunately p53 is susceptible to a single mutation. This makes it the most widely mutated gene in human cancer.

PMV Developed a Drug Designed to Target Hotspot Mutations to p53 Proteins Present in 1% of All Cancers, Potentially a Lucrative Product, if Successful

PMV Pharmaceuticals, Inc. (PMVP) is an oncology company developing a suite of small molecule, tumor-agnostic, therapies targeting the tumor suppressor protein p53. The company's lead drug candidate and only clinical-stage asset is PC14586, an oral, small molecule stabilizer and reactivator of a specific p53 point-mutation, Y220C. This point mutation is present in ~1% of all cancers, or about 75,000 newly diagnosed cases each year. There are currently no FDA approved drugs that specifically target the Y220C p53 mutation.

PMV's clinical and preclinical pipeline includes small molecule assets that target three of the top ten p53 hotspot mutations. The bull-case for the drugs and company is that this is a tumor-agnostic therapeutic approach with wide potential therapeutic applications. However, PMV's proposed therapeutic strategy has been tried before, and *it never worked*.

The p53 mutation is prolific in human cancer, so this area has been the subject of numerous academic studies. The PubMed database shows research programs targeting Y220C have been attempted since 2006. Several academic papers[3] have suggested that targeting the Y220C mutation could be a viable approach, although the lack of interest by large well-funded pharma companies speaks volumes about the results of these studies. Clinicaltrials.gov shows that **none of the candidates mentioned in these academic papers have progressed into clinical development**.

[2] See Appendix 1
[3] See Appendix 2

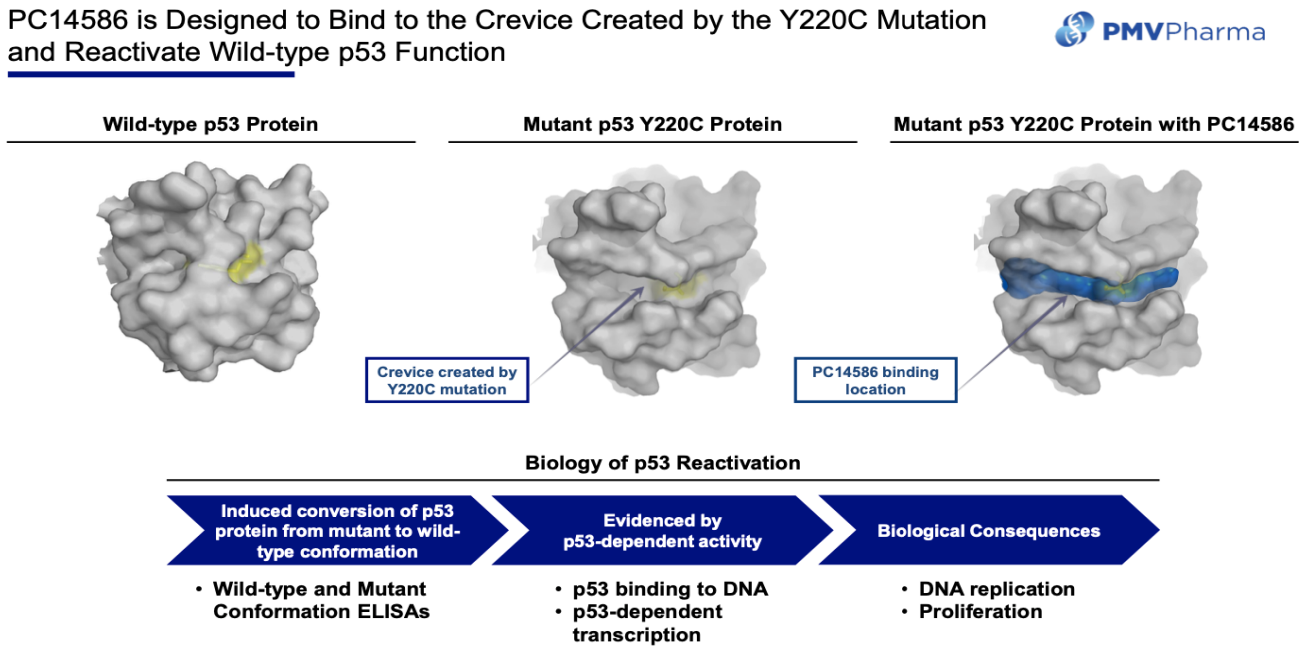
Analysis: Red Flags from PMV's Preclinical and Early Clinical Results Indicate That PMV's Leading Drug Will Fail Due to Lack of Potency and Other Deficiencies

PMV's Leading Drug Candidate Attempts to Restore Proper Cell Function to the p53 Protein

One of PMV's co-founders, Dr. Arnold Levine, was part of the initial discovery of the p53 protein in 1979. While Dr. Levine has made great contributions to medicine in his 82 years, the company he started appears now to emphasize Levine's past accomplishments over new hard data. PMV's website and investor communications are filled with general p53 information designed to intrigue retail investors but lacks current data and hard science.

Even though PMV has several different drugs in the beginning stages of development, its hopes are currently riding on one drug, PC 14586, which has advanced through the preclinical stages and into Phase I.

PMV designed PC14586 to stabilize the p53 Y220C point mutation in which tyrosine (T) is substituted by cysteine (C) at amino acid 220 of the protein. This single amino acid change creates a small crevice in the p53 protein, making it thermally unstable and unable to effectively interact with DNA. PC14586 targets this crevice with a small molecule meant to restore function to p53 Y220C.[4]



Source: PMV Pharma's Investor Presentation (Jan 2022)

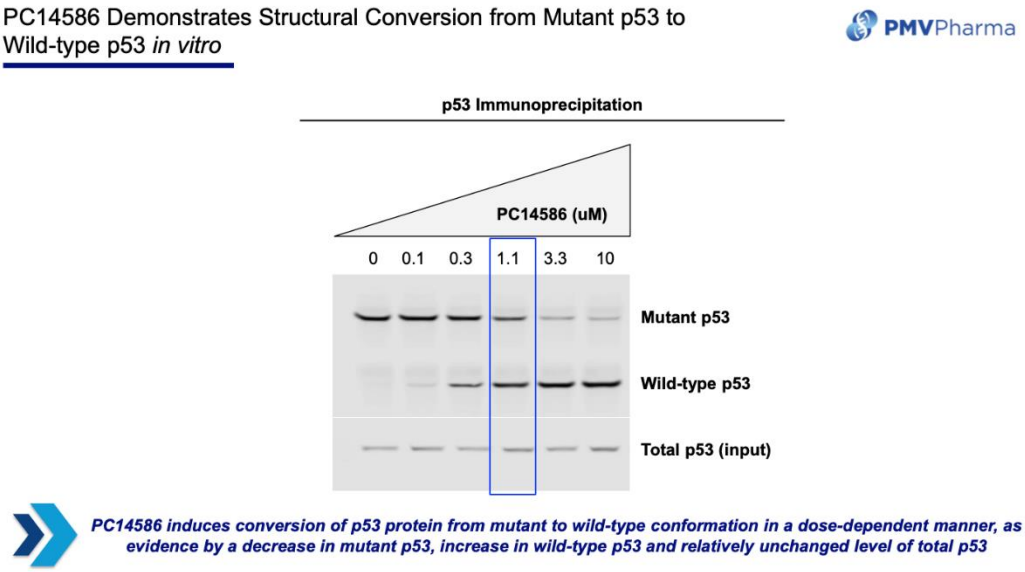
[4] PMVP, 10-K, 11, 3/1/2022

PMV calls PC14586 a “structural corrector” of p53 Y220C mutation that restores wild-type p53 function. According to PMV, “p53 Y220C mutations are found in approximately 1.0-1.5% of all cancers,”[5] with PubMed suggesting breast and ovarian are among the highest frequency. The availability of an oral small molecule selective for the p53 Y220C mutation could offer a novel precision therapy for this population.

PMV has presented data that there are low concentrations of wild-type p53 protein and an accumulation of the mutant p53 protein in the cancer cells containing the Y220C point mutation.[6] This is important because wild-type p53 is what is “guarding” from cancer.

PMV’s Preclinical Laboratory Study Results Appear to Have Been Photoshopped to Demonstrate a Concept, Instead of Clear Results

The slide below in the January 2022 Investor Presentation[7] demonstrates the apparent structural conversion of the Y220C mutated p53 protein to the wild-type protein with increasing concentrations of PC14586.



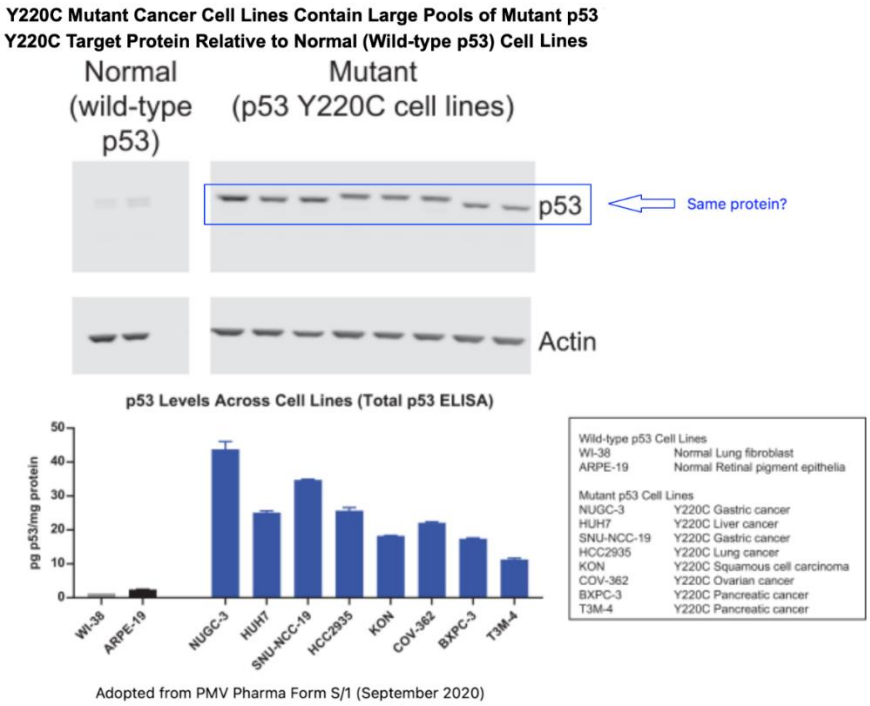
This picture is designed to show the mechanistic concept of the structural conversion from mutated to the wild-type (normal) protein, with the concentration of mutated p53 decreasing, wild-type increasing, and total p53 staying the same with escalating doses of PC14586. However, it appears **this was photoshopped to demonstrate the concept of the drug** (note the blue box we drew to show the wells are not aligned). The actual results should have lined up correctly.

[5] PMVP, 10-K, 9-10, 3/1/2022
[6] PMVP, 10-K, 10, 3/1/2022
[7] The company sent us their January 2022 investor presentation, which is not available on their website. However much of this information was reiterated in the company’s annual report. This slide was represented on page 12 of PMV’s 10-K, released on March 1, 2022.

To do this experiment, we believe researchers had to run two gels – one with protein immunoprecipitated with an antibody specific for mutant p53 and another with an antibody specific for wild-type p53. Therefore, we do not know the starting concentrations of the mutant p53, how the company identified "total p53", or if they loaded the same amount of p53 for both gels. (The company declined to speak with our consultant).

PMV's preclinical studies begin in the laboratory, where they isolate mutant p53 cell lines, place them on a gel and electrophorese the molecular agent through the gel. When this process uses the same gel, the lines should line up identically, as identical proteins should travel identical distances.

However, as we can see below, the results that PMV shared in their latest 10-K[8] did not line up, **suggesting that they are not the same protein**.



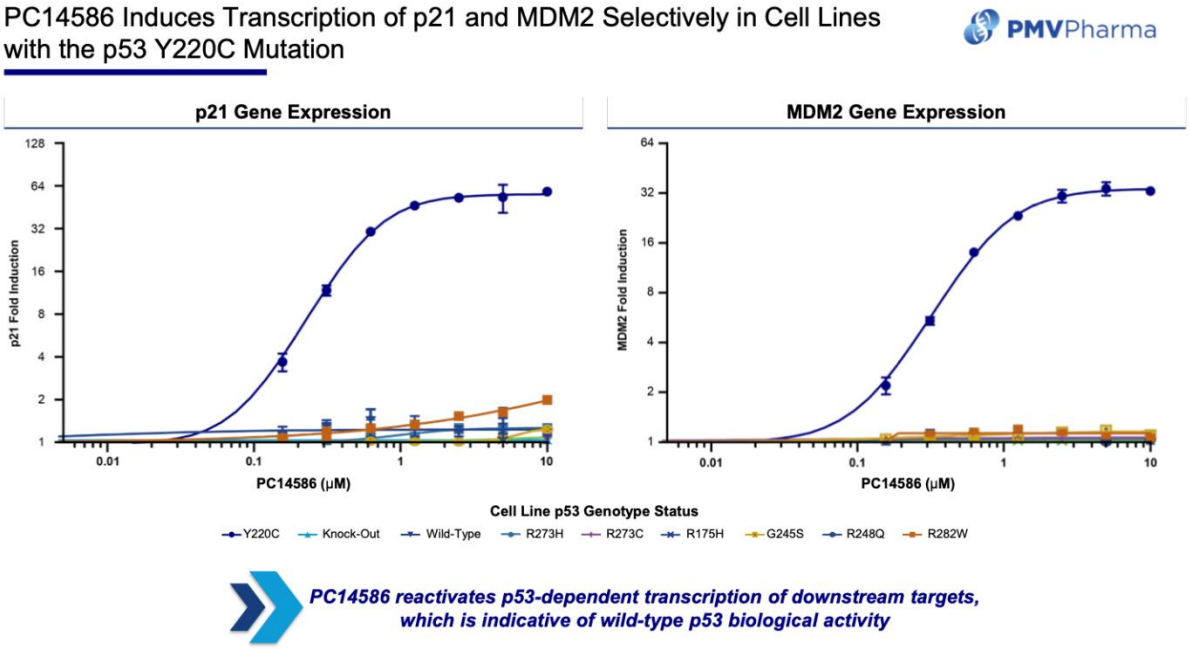
Adopted from PMV Pharma Form S/1 (September 2020)

If the Y220c p53 mutated protein is different in different cell lines, then preclinical data showing response in various cell lines become less convincing of efficacy translating to humans. In short, when researchers **cannot achieve convincing data in a petri dish, it is only getting worse with human testing.**

[8] PMVP, 10-K, 10, 3/1/2022

PMV's Preclinical Laboratory Results Indicate Their Lead Candidate Is Likely to Have Serious Side Effects

PMV claims that PC14586 only binds to the crevice created by the Y220C mutation.[9] None of the other tested p53 hotspot mutations, as illustrated by gene expression changes in the Y220C cell line when PC14586 is added in increasing concentrations should be affected. Additionally, they claim structural correction from a mutant p53 Y220C conformation to a wild-type p53 conformation by PC14586 restored p53-dependent transcription of downstream targets, [10] which would be indicative of wild-type p53 biological activity.



In an ideal scenario, everything but the Y220C (dark blue line) should appear as a flat line along the x-axis in the above chart. However, we notice that downstream gene expression of p21 and MDM2 is upregulated by PC14586, notably with concentrations as low as 0.5 µM, in cell lines with other point mutations, such as R282W. We do not see why this would occur if PC14586 is designed to only bind to the crevice found in Y220C mutations. **This calls into question the selectivity of the drug.**

[9] PMV, 10-K, 12, 3/1/2022
[10] PMV, 10-K, 12, 3/1/2022

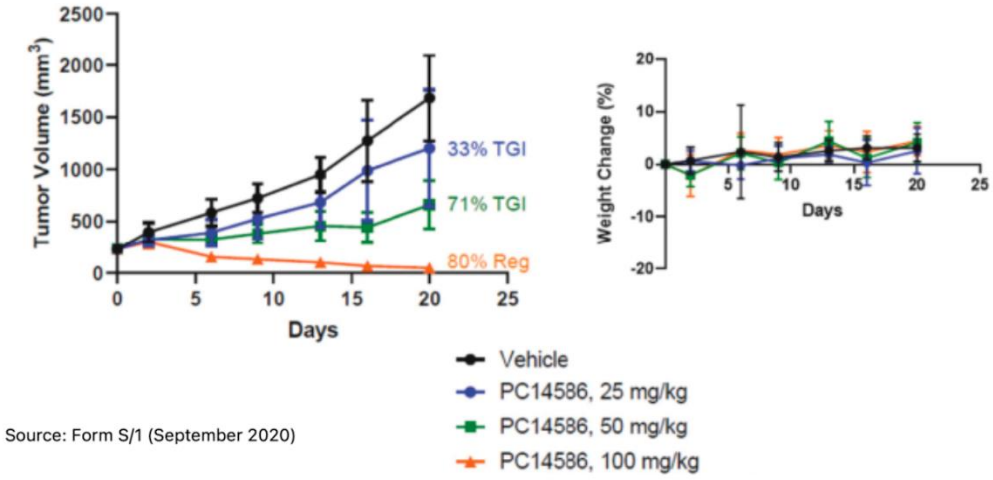
PMV's Preclinical Experiments on Mice Suggest a Competing Product Appears 100 Times More Potent than PC14586

PMV claims that PC14586 exhibited single-agent anti-tumor activity in a dose-dependent manner against mutant p53 Y220C tumors. They offered as evidence both potent TGI (see the 25 and 50 mg/kg doses) and tumor regression (see the 100 mg/kg dose).

Oral once-daily dosing over 21 days of 100 mg/kg PC14586 was tolerated in nude mice (ten mice per dosing group). These mice bore p53 Y220C mutations and tolerated the drug indicated by a lack of body weight loss, which is the generally accepted surrogate for toxicity in mice.

Remember, that the drug is currently being evaluated as a monotherapy (alone). Combinations with other medications present the potential for an additive anti-cancer effect, albeit with cumulative toxicity. Notably, it took all the way up to 100 mg/kg in a mouse model to see tumor regression.[11]

PC14586 Single-Agent Administration in NUGC3 Xenograft Model Resulted in Tumor Regression and was Well Tolerated



Source: Form S/1 (September 2020)

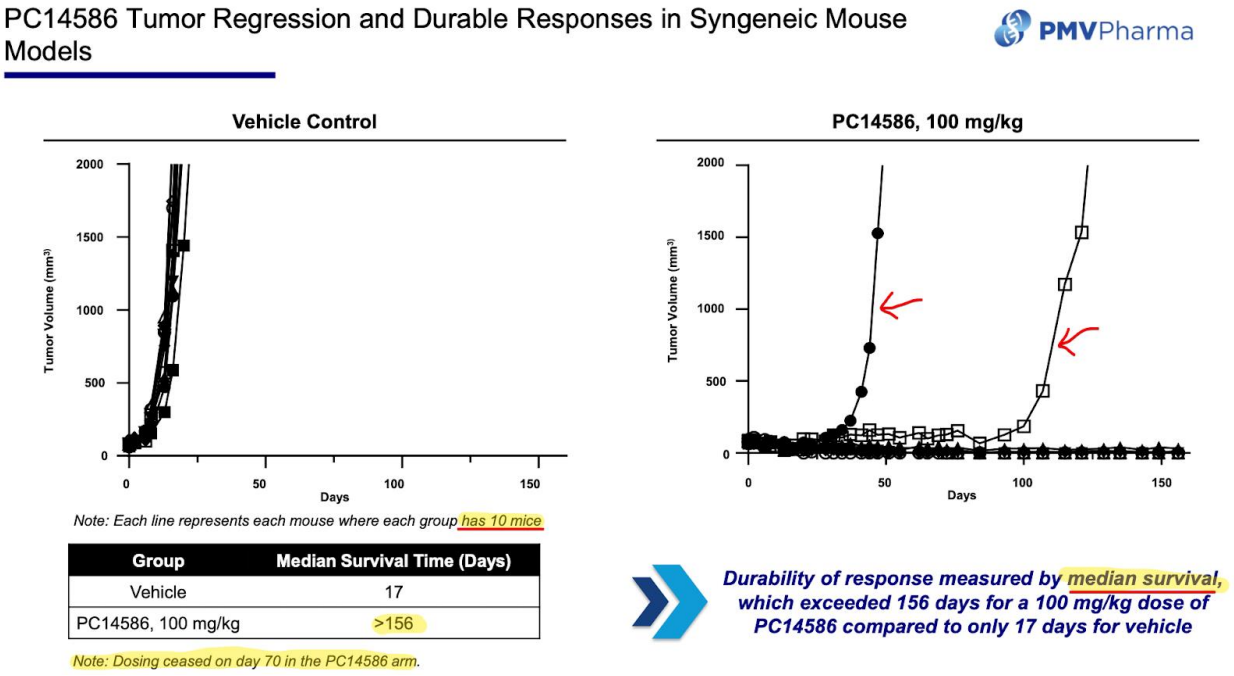
Doses less than 100 mg/kg do not look effective in generating tumor response. Using a validated practice guideline for dose conversion to humans, this converts to an effective dose of around 570 mg for a 70 kg human. This compares with FDA approved pan-cancer small molecules such as ibrutinib (recommended daily dose for MCL and MZL is 560 mg QD (daily), sorafenib (400 mg BID (2x daily) for HCC), and venetoclax (400 mg QD for CLL), but all these agents showed effective tumor regression in mouse models at far lower doses. Moreover, **all these agents have significant toxicity issues**.

[11] Represented in 10-K, 13, 3/1/2022

These preclinical tests on mice indicate that PC14586 is not a very potent drug and may have a small therapeutic window. The IC50 (a standard measure of potency) for various cell lines ranges between 0.192 µM to over 8.6 µM.[12] For reference, Kymera Therapeutics reported that KT-253, its novel MDM2 protein degrader designed to restore wild-type p53 activity, has IC50 in the picomolar range and resulted in regression of tumor cell growth in preclinical models with dosage as low as 1 mg/kg.[13] ***Kymera's drug appears to be at least 100x as potent as PMV's leading drug candidate*.**

Some of PMV's Preclinical Mice Studies Raise Red Flags About the Selectivity of the Data Presented

PMV has presented mouse data that looks impressive, at least initially. At a 100 mg/kg dose, mice treated with their leading drug candidate had a median survival of >156 days versus only seventeen days for the vehicle.[14]

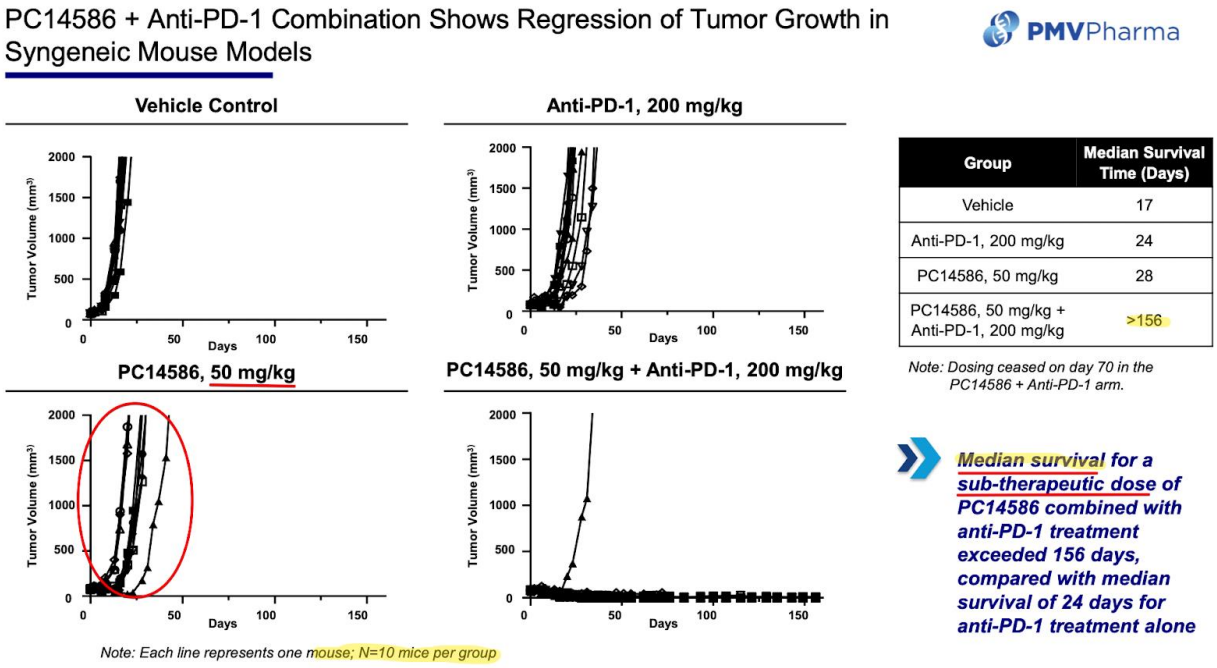


However, the fine print of the slide tells us that this is the *median* survival for a group of ten mice in each model group. The exact model for each group is not disclosed. This highly limited inclusion of results makes it difficult to gauge the target tumor types and the response rates. It is not really data manipulation or obfuscation, but it's unusual to release such selective data.

[12] Discussed in PMV's Patent, WO2021262483A1, page 2,535.
[13] Kymera, Press Release, 4/8/2022
[14] Originally presented in Jan 2022 presentation, represented in 10-K, 15, 3/1/2022

PMV's Synergistic Tests Indicate Its Leading Candidate Is Ineffective at Low Doses

Another slide shows us their leading drug candidate's synergy with anti-PD-1.[15] This model is described as a "cold tumor" model, meaning immunotherapy is not expected to show activity, so response from anti-PD-1 is not expected. PMV used a sub-therapeutic dose of PC14586 at 50 mg/kg and the results show a dramatic lack of response (vs. the supposed 100 mg/kg therapeutic dose level). However, when PC14586 is dosed with anti-PD-1, there is an impressive improvement in median overall survival to >156 days.



As in the previous slide, the data is for the median of a group of ten mice, and we are not told the specific models used. What concerns us most is the lack of response for the 50 mg/kg dose. This indicates the drug **lacks potency until it gets up to high doses**.

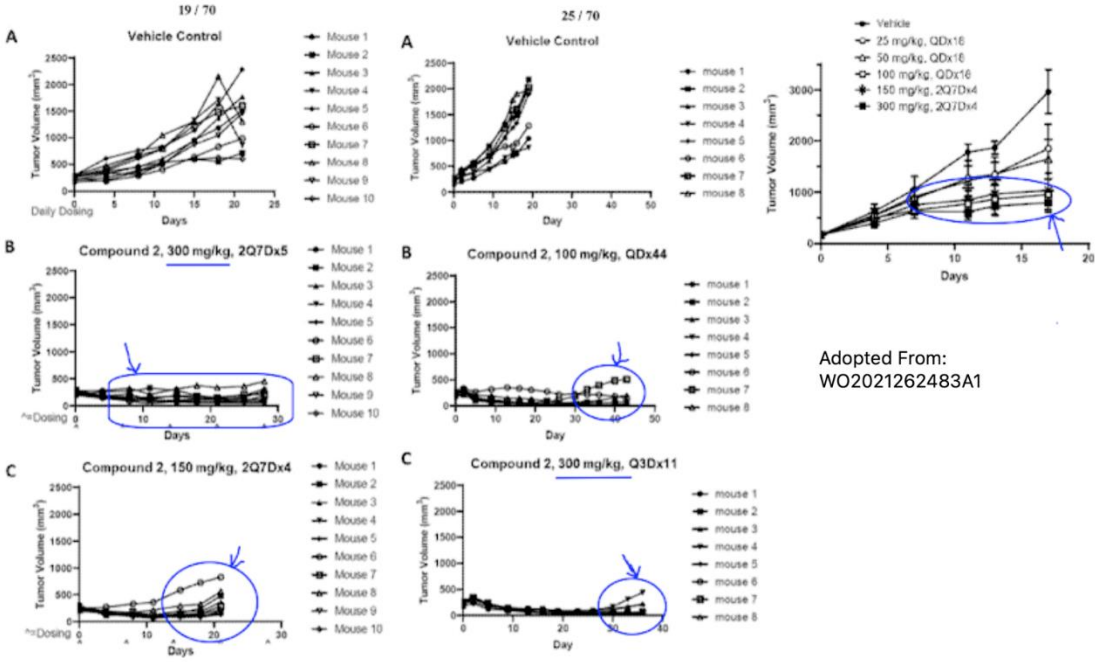
We would also point out that for the FDA to approve this drug, PMV will need to show that it can be efficacious in humans as a monotherapy at tolerable doses.

As far as the impressive efficacy of the combination, we are not told anything about the rationale for this mechanism. The company does not say why reactivating p53 results in "turning cold tumors hot" (enhancing immunotherapy), nor do they say anything about the potential toxicity. This lack of tumor growth is not necessarily from on-target synergistic effects and could be associated with overt toxicity.

[15] Represented in 10-K, 15, 3/1/2022

Additional Data from Mice Indicate That PMV's Leading Drug Candidate Lacks Potency

Some additional mouse model data can be found in the patent.[16] These data reinforce our concerns about the potency of the drug, **with doses as high as 300 mg/kg needed just to maintain tumor size** (i.e., stable disease).



PMV Pharma is conducting a Phase 1 healthy volunteer study to investigate the food effects on dosing (NCT05249348) (this determines if a drug should be taken with or without food). It is curious that the company has progressed into a Phase 1/2 dose-escalation study (NCT04585750) before fully understanding the pharmacokinetics of the drug.

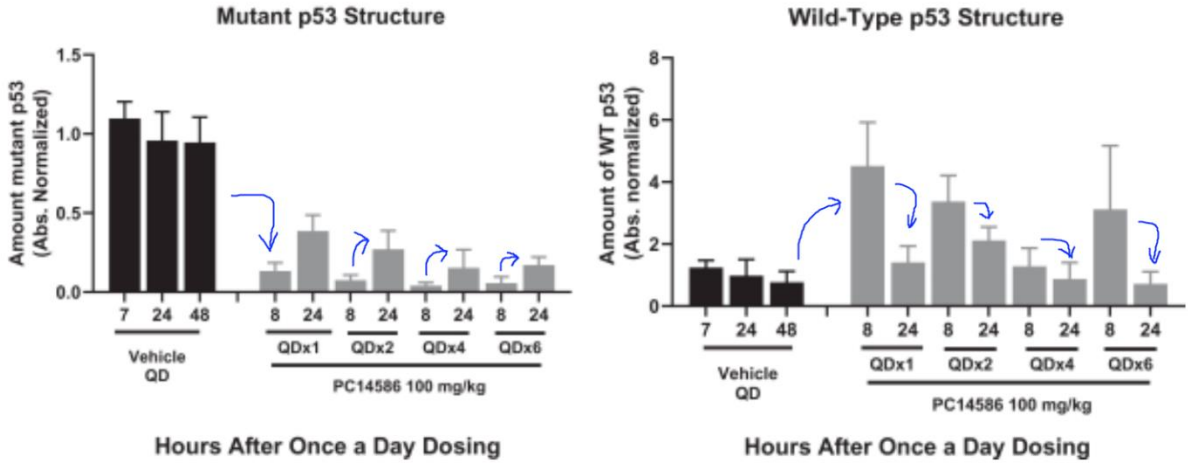
PMV's Lead Drug Candidate Has a Narrow Therapeutic Window, Indicating That the Drug May Not Restore Normal Cell Function Long Enough to Generate Durable Tumor Regression in Humans

The half-life of PC14586 at 100 mg/kg is reported to be ~7.5 hours[17]. This short half-life of the drug is a concern. PC14586 needs to be administered daily (QD) at doses greater than 570 mg. PC14586 knocks down mutant p53 ~8 hours after an oral dose, as expected, but the level bounces back to roughly half the pre-dose level at 24 hours.[18]

[16] Patent, WO2021262483A1, 536-538.
[17] Patent, WO2021262483A1, Table 71
[18] PMVP, 10-K, 13, 3/1/2022

However, more important than the level of mutant p53, from a cancer-fighting mechanism standpoint, is the level of "restored" wild-type p53 active. This can be seen on the right in the figure below.[19]

In *in vivo* Studies, PC14586 Converted Mutant p53 Protein to a Wild-type p53 Structure



Source: Form S/1 (September 2020)

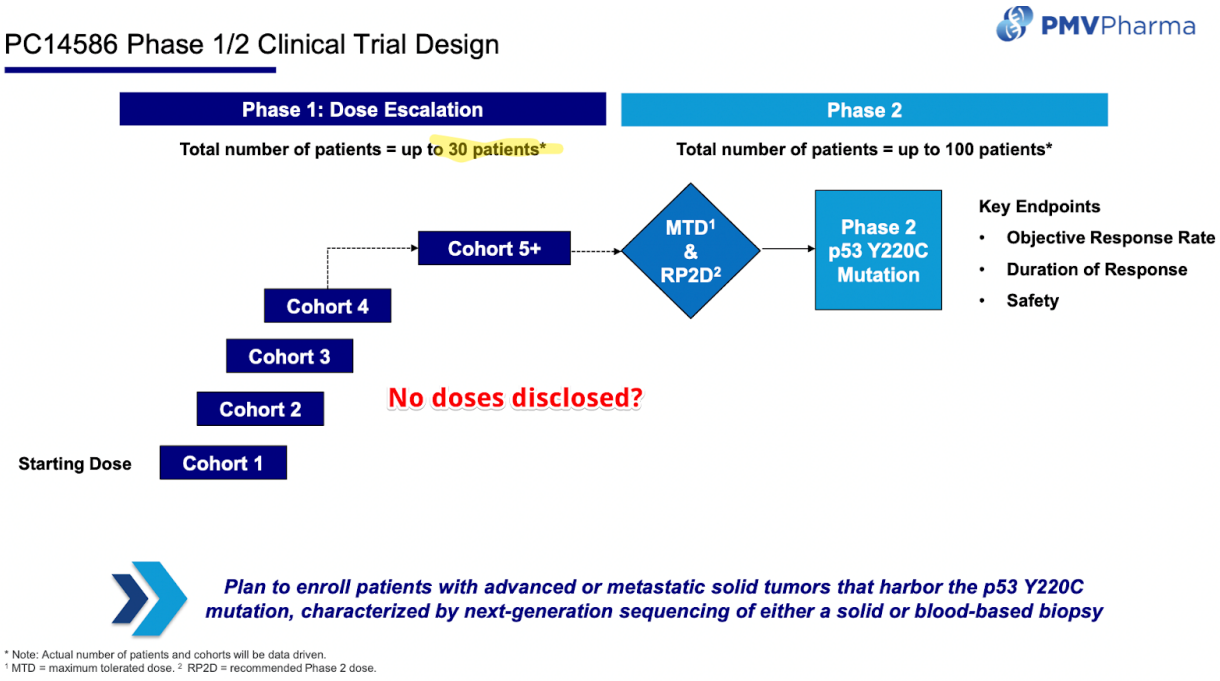
Wild-type p53 activity increases approximately five-fold ~8 hours after the first oral dose. However, **by 24 hours, the activity is back down to pre-dose levels.** The effect of the drug seems to be diminished after a few days of daily oral dosing. By Day-6, the increase in wild-type p53 activity is lower than on Day-1, and that is with a huge error bar that suggests high variability among samples. The wild-type p53 activity by 24 hours after the Day-6 dose is virtually identical to the pre-dose level on Day-0.

We are not convinced that PC14586 can raise wild-type p53 activity high enough, for long enough, to effectively restore normal cell function or to result in durable tumor regression in humans.

[19] PMVP, 10-K, 14, 3/1/2022

The Results of PMV's Phase I Dose Escalation Study Have Been Delayed, But Select Non-Public Data Shared with Sell-Side Analysts Indicate That the Drug Lacks Potency in Humans

In November 2020, PMV Pharma initiated a Phase I dose-escalation study of PC14586 in patients with advanced solid tumors and Y220C mutated p53. The goal of this portion of the Phase 1/2 trial is to identify a maximum tolerated dose (MTD) and recommended dose to move into the Phase 2 (RP2D) expansion studies in select target indications. And yet, the company has provided minimal updates on the dose-escalation study over the past 17 months.



In April 2021, at the American Association for Cancer Research (AACR) annual meeting, PMV Pharma's SVP of Preclinical Development and Translational Science, Melissa Dumble, PhD, presented the research around PC14586 and the current Phase 1/2 study in a short video. During the video, Dr. Dumble noted initial data were expected soon, "By the end of the year or early next year." More information can be found in an abstract published in the AACR journal in July 2021.

We are concerned by the lack of disclosure around the ongoing Phase 1 study. This is an open-label study, and the **lack of updates and missing initial guidance** is not a good sign. Moreover, and this should matter to the SEC, although management is not talking publicly about the data, they are apparently sharing information with select sell-side analysts:

about 1%-1.5% in solid tumors. Mgmt had previously noted that the 600 – 1200 mg QD dose could enter PC14586's therapeutic window in the clinic based on allometric scaling while caveating that more recent PK-exposure modeling suggested the window could potentially start at 1000 – 2000 mg QD. Importantly, Mgmt also stated that they have been

We recently (3/22) caught up with mgmt, who provided incremental color around potential cadence of data disclosures leading up to ASCO 2022 (caveat that abstract acceptance notifications are still pending). PMVP noted that abstract data may still be early & limited given submission deadlines that are months before a potential final data cut. Upon release of abstract data, mgmt may also issue a concurrent press release, potentially with additional incremental color. Following the ASCO presentation, PMVP may host an investor or KOL event either at or after the conference to review the full results. Separately and in parallel, PMVP noted it was putting together a protocol amendment to enroll beyond N=30 patients currently allowed in the Phase I with the goal of adding more patients at what mgmt thinks could be potential RP2D heading into Phase II single-agent expansions, now with potential initiation by YE 2022 (previously 2H 2022). That said, mgmt caveated that these additional patients under potential protocol amendment would likely not be presented at ASCO.

Source: Guggenheim research report, 3/22 (found on Twitter)

There are several red flags here. First, it seems efficacy has not been observed at the initial therapeutic dose of 600 to 1200 mg QD. If there were notable efficacy, one would expect a substantive update saying so. Recall, that this is the level initially hypothesized by the 100 mg/kg mouse data. Second, escalating to doses above 1 gram per day is a serious concern, and not only with respect to the size or number of the pills. We are hard-pressed to find similar oral cancer drugs dosed at this elevated level.

We are concerned that the minimally effective dose (MED) is too near the maximum tolerated dose (MTD), a problem that historically has been a challenge for oral anti-cancer drugs.

As a general rule, single-agent activity is a must in the eyes of the FDA. The narrow therapeutic window and lack of selectiveness for this drug is highly problematic. PMV Pharma must demonstrate PC14586 is both effective and tolerable as monotherapy before they start looking at combinations.

These whispers to the sell-side analysts also contain the worrisome news that PMV is expanding the initially targeted N=30 per cohort, adding more patients before identifying the RP2D. It seems that management is dragging more and more patients into the trial as they hunt farther and wider for signs of efficacy.

PMV is scheduled to present data at the American Society of Clinical Oncology (ASCO) meeting on June 7th, 2022. Their abstract should be released on May 26th. A benchmark for efficacy as a monotherapy in this population is at least 25% overall response rate, with the durability of response at or beyond six months.

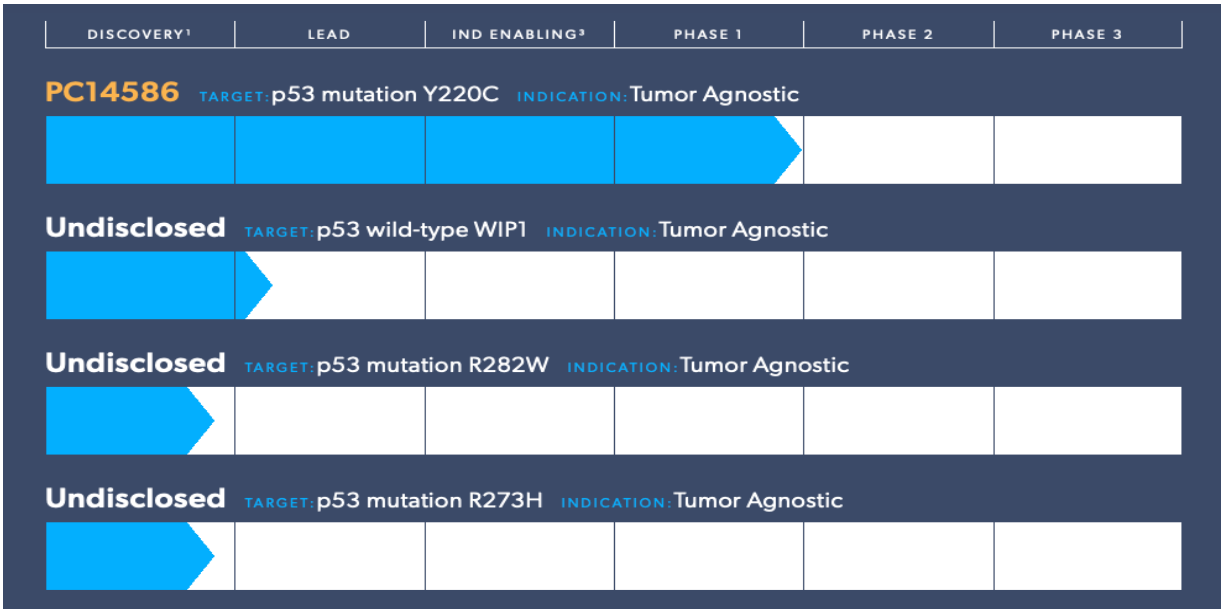
We believe investors will react negatively to any update suggesting PMV Pharma has not identified a dose that can achieve this level. The potential for a disappointing update at ASCO is the looming catalyst for shorting the stock at today's price.

PMV's Management Is Already Moving on to a New Approach

When PMV Pharma filed the Form S/1 (September 2020), the company noted two additional programs beyond PC14586, each targeting hotspot mutations in p53, R273H and R282W. The S/1 suggested that the program targeting R273H was moving into lead optimization in the first half of 2021.[20]

We expect to advance our next program, targeting the p53 R273H hotspot mutation, into lead optimization in the first half of 2021.

However, as of the most recent Investor Presentation (and Pipeline chart shown on the company's website), neither the R273H nor the 282W programs show candidates in lead optimization.



We believe the most likely explanation for this delay is a lack of encouraging signs seen from the ongoing Phase 1/2 study with PC14586, and since these two drugs are very similar to the lead candidate, these drugs in all probability are a bust.

Instead PMV has moved a new drug candidate into pole position, one that targets WIP1 (wild-type p53 induced phosphatase). WIP1 is a gene target that reduces wild-type p53 levels and negatively regulates the DNA damage response pathway. This is a completely different mechanism of action and strategy from targeting hotspot mutations such as Y220C, R273H, and/or R282W.

This delay in advancing additional hotspot mutation programs and the shift in strategy to focus on alternate pathways to improve wild-type p53 activity can only be seen as an additional red flag. To us it signals plainly that PC14586 is not living up to expectations in the current Phase 1/2 study**.**

[20] PMVP, S1, 134, 9/4/2020

Conclusion: PMV's Lead Drug Candidate Will Likely Fail Due to Lack of Potency, A Dire Result for Investors

PMV's lead candidate reminds us of Aprea's failed efforts with eprenetapopt (APR-246), a small molecule designed to reactivate mutant and inactivated p53 protein. Aprea's drug failed to show a statistically significant improvement on top of chemotherapy drug azacitidine in patients with p53 mutant myelodysplastic syndromes (MDS) in late 2020.

The lack of positive outcomes resulted in the FDA placing two separate clinical holds on further development of the drug for combinations with other anticancer agents for potential toxicity concerns in 2021. The market did not like this:

We expect the market to have a similar response if PMV's data demonstrates that the drug lacks the potency necessary for it to be approved by the FDA as an effective monotherapy.

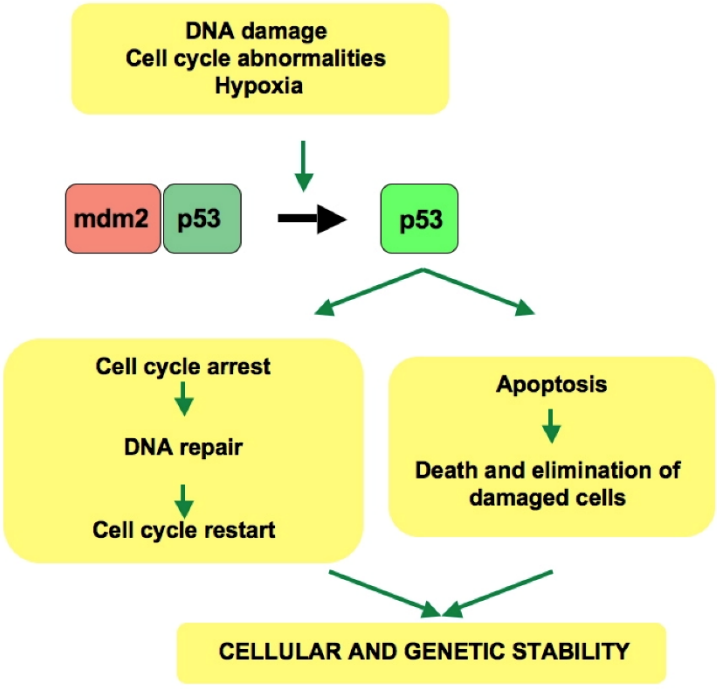
PMV Pharma is currently trading at $13.77 per share, which equates to a market capitalization of approximately $628 million. PMV exited March 2022 with $295 million in cash, with a cash burn of approximately $18 million last quarter.

We believe that PMV's lead candidate will prove worthless, along with the similarly designed programs targeting R282W and R273H. At this stage, assigning any value to the WIP1 program is pure speculation.

Targeting mutant p53 has been a difficult area for biopharma investors. We believe in just a matter of a few days, PMV Pharma will head down the same path as Aprea, its stock dropped 77% on the Phase 3 failure in December 2020.

Appendix 1

In healthy cells, p53 is kept dormant by its negative regulator, MDM2. However, upon DNA damage or other cell-cycle abnormalities, the p53 / MDM2 relationship changes and p53 becomes active. Once activated, p53 induces a cell-cycle arrest at the G1/3 phase. This allows it to either repair and promote the survival of the cell, or it can initiate apoptosis through programmed cell death. The latter option clears away the damaged or cancerous cell if a repair cannot be made.



Appendix 2

Several research programs targeting Y220C have been attempted since 2006.

A structure-guided molecular chaperone approach for restoring the transcriptional activity of the p53 cancer mutant Y220C

Bauer, Matthias R.; Jones, Rhiannon N.; Tareque, Raysa K.; Springett, Bradley; Dingler, Felix A.; Verduci, Lorena; Patel, Ketan J.; Fersht, Alan R.; Joerger, Andreas C.; Spencer, John

Future Medicinal Chemistry (2019), 11 (19), 2491-2504CODEN: FMCUA7; ISSN:1756-8919. (Future Science Ltd.)

Aim: The p53 cancer mutation Y220C creates a conformationally unstable protein with a unique elongated surface crevice that can be targeted by mol. chaperones. We report the structure-guided optimization of the carbazole-based stabilizer PK083. Materials & methods: Biophys., cellular and x-ray crystallog. techniques have been employed to elucidate the mode of action of the carbazole scaffolds. Results: Targeting an unoccupied subsite of the surface crevice with heterocycle-substituted PK083 analogs resulted in a 70-fold affinity increase to single-digit micromolar levels, increased thermal stability and decreased rate of aggregation of the mutant protein. PK9318, one of the most potent binders, restored p53 signaling in the liver cancer cell line HUH-7 with homozygous Y220C mutation. Conclusion: The p53-Y220C mutant is an excellent paradigm for the development of mutant p53 rescue drugs via protein stabilization. Similar rescue strategies may be applicable to other cavity-creating p53 cancer mutations.

Small molecule induced reactivation of mutant p53 in cancer cells

Liu, Xiangrui; Wilcken, Rainer; Joerger, Andreas C.; Chuckowree, Irina S.; Amin, Jahangir; Spencer, John; Fersht, Alan R.

Nucleic Acids Research (2013), 41 (12), 6034-6044CODEN: NARHAD; ISSN:0305-1048. (Oxford University Press)

The p53 cancer mutant Y220C is an excellent paradigm for rescuing the function of conformationally unstable p53 mutants because it has a unique surface crevice that can be targeted by small-mol. stabilizers. Here, we have identified a compd., PK7088, which is active in vitro: PK7088 bound to the mutant with a dissocn. const. of 140 μM and raised its melting temp., and we have detd. the binding mode of a close structural analog by X-ray crystallog. We showed that PK7088 is biol. active in cancer cells carrying the Y220C mutant by a battery of tests. PK7088 increased the amt. of folded mutant protein with wild-type conformation, as monitored by immunofluorescence, and restored its transcriptional functions. It induced p53-Y220C-dependent growth inhibition, cell-cycle arrest and apoptosis. Most notably, PK7088 increased the expression levels of p21 and the proapoptotic NOXA protein. PK7088 worked synergistically with Nutlin-3 on up-regulating p21 expression, whereas Nutlin-3 on its own had no effect, consistent with its mechanism of action. PK7088 also restored non-transcriptional apoptotic functions of p53 by triggering nuclear export of BAX to the mitochondria. We suggest a set of criteria for assigning activation of p53.

Aminobenzothiazole derivatives stabilize the thermolabile p53 cancer mutant Y220C and show anticancer activity in p53-Y220C cell lines

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Many cancers have the tumor suppressor p53 inactivated by mutation, making reactivation of mutant p53 with small mols. a promising strategy for the development of novel anticancer therapeutics. The oncogenic p53 mutation Y220C, which accounts for approx. 100,000 cancer cases per yr, creates an extended surface crevice in the DNA-binding domain, which destabilizes p53 and causes denaturation and aggregation. Here, we describe the structure-guided design of a novel class of small-mol. Y220C stabilizers and the challenging synthetic routes developed in the process. The synthesized chem. probe MB710, an aminobenzothiazole deriv., binds tightly to the Y220C pocket and stabilizes p53-Y220C in vitro. MB725, an ethylamide analog of MB710, induced selective viability redn. in several p53-Y220C cancer cell lines while being well tolerated in control cell lines. Redn. of viability correlated with increased and selective transcription of p53 target genes such as BTG2, p21, PUMA, FAS, TNF, and TNFRSF10B, which promote apoptosis and cell cycle arrest, suggesting compd.-mediated transcriptional activation of the Y220C mutant. Our data provide a framework for the development of a class of potent, non-toxic compds. for reactivating the Y220C mutant in anticancer therapy.

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