Evaluate Vantage

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Asco 2022 – PMV's therapeutic window slams shut

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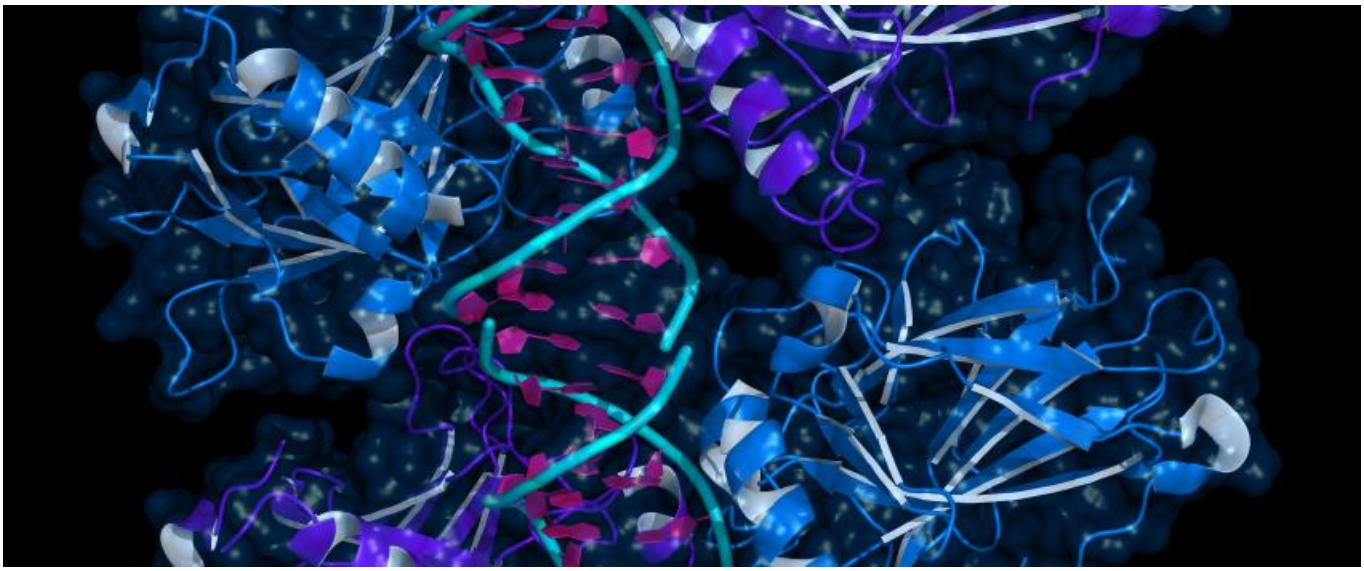


Liver and other toxicities threaten to scupper another attempt to reactivate mutated p53, the "guardian of the genome".

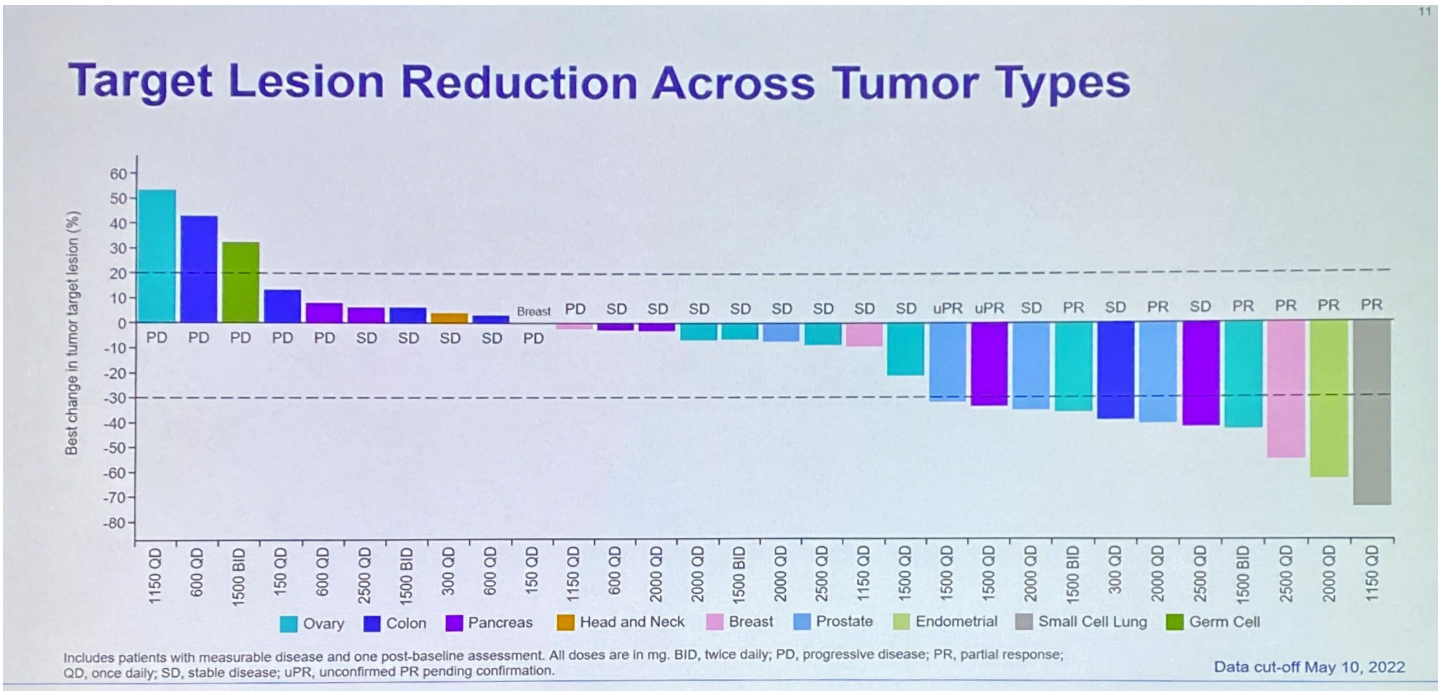
What goes up must come down, as PMV Pharmaceuticals investors discovered today. As one of the biggest gainers at the time of the Asco abstract drop the company came into the conference with much to prove. Unfortunately, a presentation today suggested that its p53 reactivator PC14586 might not have a viable therapeutic window.

Nevertheless, both the presenter of the study in question, Pynnacle, and its Asco discussant hailed the result as proving that p53 was becoming druggable. But this ignores toxicities that threaten the most active PC14586 dose, and with PMVP stock off 22% today the company might soon be joining others that have failed with this highly intractable target.

On the positive side, the Pynnacle study presenter, Dr Ekaterina Dumbrava of MD Anderson, cited eight partial remissions among 31 subjects with p53-mutant cancers given PC14586 at high doses of 1.15-2.5g daily and 1.5g twice daily. There were no responses in the 10 given lower 150-600mg once-daily doses.

However, across the 41-patient set she cited liver enzyme increases – nine involving aspartate aminotransferase and eight alanine aminotransferase. There were also severe cases of hypokalaemia and pneumonitis, and two dose-limiting toxicities at 1.5g twice daily: one grade 3 AST/ALT increase and one grade 3 acute kidney injury.

And this is where the PMV story unravels. A close look at the waterfall plot reveals two of the eight remissions to be unconfirmed – both appearing to be at the borderline of what can be classified as a PR. And of the six confirmed PRs, five were achieved with the highest PC14586 dosing of 2-2.5g daily or 1.5g twice daily.



Source: Dr Ekaterina Dumbrava & Asco.

The discussant, Dr Irene Brana of Vall d'Hebron Institute of Oncology, gave a resounding “yes” to the question of whether p53 can now be drugged. Whether this can be achieved at a dose that does not cause unacceptable toxicity is the question PMV now has to grapple with.

p53 was first identified in 1979, and has been a “holy grail” in oncology drug discovery; it is a tumour suppressor protein with a central function in numerous critical cell processes, and is sometimes called the “guardian of the genome”. Its inactivation – either by mutation of the *TP53* gene or by other means – is estimated to be a factor in over half of all cancers.

But targeting it has proved elusive. PC14586 is said to work by stabilising a key p53 mutation, and thus restoring this protein’s normal function.

MDM2 amplification

p53 can also become inactivated by other factors, such as overexpression of the MDM2 protein. MDM2 is a negative regulator of p53, and cancers driven by this process are called p53 wild-type, since here p53 remains unmutated.

This calls for an entirely separate mechanistic approach. And this is where companies including Kartos Therapeutics and Boehringer Ingelheim come in with MDM2 antagonists, specifically navtemadlin and BI 907828 respectively. Both assets also featured at Asco oral sessions over the weekend.

Navtemadlin yielded early data from p53 wild-type Merkel cell carcinoma patients who had failed PD-(L)1 blockade. Most of its activity seemed to be in those who had not received chemotherapy, with six PRs (one of which was unconfirmed) seen across 15 subjects. In 14 post-chemo subjects there were just two unconfirmed remissions, though one non-responder was later found to have a p53 mutation.

Meanwhile, BI 907828 showed some activity in p53 wild-type liposarcoma, specifically in de-differentiated disease (four PRs in 28 subjects) and well-differentiated disease (four PRs in 15). Boehringer is now enrolling patients into the phase 2/3 Brightline-1 study in front-line de-differentiated liposarcoma, while Kartos plans to begin pivotal dose-expansion at the recommended phase 2 dose in the second half.

Other MDM2 inhibitors in clinical trials include Ascentage’s APG-115, Rain Therapeutics/Daiichi Sankyo’s milademetan, Novartis’s siredmadlin, Aileron’s ALRN-6924 and Astex’s ASTX295.

Still, those interested in mutated p53-driven cancer will recall Aprea, a group that had styled itself as the p53 reactivation company. Its lead asset, eprenetapopt, flunked phase 3 in front-line p53-mutant myelodysplastic syndromes and then was hit with two clinical holds.

Aprea became a listed shell into which the private group Atrin reversed last month. Though work on p53 is no longer a primary focus APR-548, an improved form of eprenetapopt, is in phase 1. Meanwhile, another company that had focused on p53 was the private San Diego group Actavalon, which no longer seems to be active.

The big worry for PMV investors is that their company now risks joining Aprea and Actavalon on the list of p53 reactivation disappointments.

This article has been corrected to add Rain as the licensee for milademetan.