Evaluate Vantage

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Aprea’s p53 dream is now officially a nightmare

Jacob Plieth

Malfunctioning of the p53 protein, sometimes called the guardian of the genome, hasfor decades been implicated in cancer. Efforts to target it, however, have proved elusive, as Aprea seems pretty unequivocally to have found out. The biotech’s lead asset, the p53 “reactivator” eprenetapopt, flunked phase 3 in front-line TP53-mutant myelodysplastic syndromes last December, since when Aprea has been working hard on subgroup analyses, recently putting the failure down to undertreatment in the experimental cohort. However, eprenetapopt has now been slammed with not one but two clinical holds. Last week the FDA halted an azacytidine combo trial in AML and myelodysplastic syndromes, and today a similar fate befell a CLL/lymphoma trial, in combination with Calquence or Venclexta. The first hold was due to increased serious adverse events versus control, including a fatality, and the second seems to be an extension. With Aprea’s stock now off 85% since December investors will wonder where the eprenetapopt setbacks leave APR-548, a next-generation, oral p53 reactivator that was to have entered phase 1 last quarter. Other p53 players, including PMV Pharma, Actavalon and Aileron Therapeutics, will also cast a nervous eye over developments.

Selected Aprea trials of eprenetapopt (APR-246)			
Study	**Disease**	**Design**	**Status**
NCT03745716	TP53mut MDS	Ph3 azacitidine combo, vs azacitidine	Failed: CR rate 33% vs 22% for control
NCT03931291	TP53mut AML & MDS	Azacitidine combo	On partial clinical hold
NCT04419389	Lymphomas & CLL	Calquence or Venetoclax+Rituxan combo	On clinical hold
NCT04383938	Solid tumours	Keytruda combo	Continuing to enrol
Source: company statements.			