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Interview – Aprea takes aim at new cancer target

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A $51m fundraising is an impressive feat for a European company yet to go into phase II trials. But Aprea's lead product, a small molecule p53 modulator, has the potential to treat half of all cancer cases, the Swedish group believes – making the gamble more understandable.

"p53 is by far the most mutated gene in human cancers," Aprea's executive chair Bernd Seizinger tells *EP Vantage*. "About 50% of all human cancers have p53 mutations." These mutations inactivate the p53 pathway, which has a role in killing damaged cells – defective p53 allows abnormal cells to grow, leading to cancer.

The idea is that APR-246 could restore this pathway by fixing the mutant p53 protein's conformation and "reactivating all its tumour suppressor function", explains Dr Seizinger.

Identifying those with the mutation in question should be relatively simple with the advent of cheap gene sequencing, he adds.

Elusive target

A drug targeting p53 could be particularly useful as patients with mutations have a poor overall survival "and are oftentimes quite resistant to a number of anticancer drugs", says Dr Seizinger.

But development has been far from easy – the target was first identified in 1979. "p53 has been the holy grail in oncology drug discovery for two decades, but it has been quite elusive," he says.

He adds that in a previous role at Bristol-Myers Squibb he did not succeed in identifying a suitable candidate. "We didn't find it, Merck didn't find it, many other companies small and large who have looked for it didn't find it."

Dr Seizinger believes that APR-246 is the first molecule to directly interact with the mutant p53 protein; it certainly appears to be the only drug in clinical trials to do so.

Other companies have taken an indirect approach, including Critical Outcomes Technologies, which has a protein kinase inhibitor, Coti-2, in phase I. "It seems to have some effect on restoring p53 activity, but it's an indirect activity whose mechanism is not directly understood," Dr Seizinger says.

PMV Pharma is also focused on p53 modulators, but these appear to be at the preclinical stage.

Meanwhile Aprea's APR-246, based on a discovery by the Karolinska Institute, is soon to move into the phase II portion of a phase Ib/II study in ovarian cancer, its most advanced indication.

The company chose this disease for various reasons, according to Dr Seizinger, including the high rate of p53 mutations – around 60% in ovarian cancer overall, rising to 95% in high-grade serous disease – and the fact there is a large unmet need. The lack of current options should mean one phase III trial is enough for approval, and would help APR-246 carve out a niche once approved.

With the latest cash injection, Aprea is financed until 2019 when the phase II results are due to report – the main goal is to show an improvement in progression-free survival.

"The most likely scenario, if the data look good, will be a trade sale of the company," says Dr Seizinger. "An alternative could also be an IPO on Nasdaq."

To this end, Aprea is using some of the proceeds from the fundraising to beef up its presence in the US, with its strategic leadership team likely to be based on the East Coast in future. It is not a coincidence that the series B round was co-led by US investors Versant Ventures and 5AM Ventures.

Livin' on Aprea

But ovarian cancer "is only really the tip of the iceberg for this drug", according to Dr Seizinger. Some of the funds will go towards parallel exploratory trials "in a number of other indications" encompassing haematological and solid tumours.

These could include acute myeloid leukaemia. “In AML the frequency of p53 mutations is not very high, about 5-15%, but if it does occur these patients have a very devastating prognosis,” says Dr Seizinger. “They are resistant to most anticancer drugs and their overall survival is much shorter.”

This might allow “some potential shortcuts for accelerated approval” in AML or other indications with a similar unmet need, he adds.

APR-246 could also be combined with other agents, including checkpoint inhibitors. Intriguingly, APR-246, like wild type p53, has been shown to activate another gene, microRNA-34a, which has recently been shown to inhibit PD-L1.

“There’s clearly a scientific link. What we’re beginning to do now is check whether there’s synergy between APR-246 and the checkpoint inhibitors,” says Dr Seizinger.

Aprea clearly has big ambitions. If APR-246 is shown to solve the problem of p53 mutations, it could soon also have some of the big players knocking on its door.

Trial	Details	ID
Pisarro	Phase Ib/II study in high-grade serous ovarian cancer in combination with carboplatin chemotherapy	NCT02098343

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