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Sachs Forum – Deciphering the immunology combo avalanche

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As the nearly 800 currently ongoing studies involving anti-PD-(L)1 agents combined with other approaches speed towards readout investors will be faced with a tough question: how precisely to interpret the overwhelming amount of data generated.

The issue took centre stage at a panel discussion at today's Sachs Associates Immuno-oncology Forum on the sidelines of the Asco meeting. It will be one of several things the industry will grapple with, though it is by now abundantly clear that there is no stopping the combo study runaway train.

That fact was illustrated in a report just published by *EP Vantage*, which showed that the absolute number of anti-PD-(L)1 combo trials under way – with numerous mechanistic approaches – had surged nearly fourfold since November 2015 to reach 765 in April.

Dr James Mulé, from the Moffitt Cancer Center, told the Sachs conference that it was hard to imagine just how rapidly these trials were being conducted. In terms of subjects enrolled, he cited data showing that there were now over 250,000 patients in active immuno-oncology studies.

"But there will be no clear-cut direction as to where combo studies are heading until about 2019," he said. "There's still a way to go before we can make clear-cut decisions."

John Beadle, chief executive of Psioxus, whose oncolytic virus enadenotucirev is being combined with Bristol-Myers Squibb's Opdivo, called the expected surge of data an "exponential avalanche of information".

Still, most of these studies are too early to involve randomisation, and many are not designed to answer the simple, head-to-head question of whether A plus B is better than A or B alone. And, while it is clear than many combos will not work, what yardsticks should investors use to determine whether a combination has actually given an incremental benefit?

The panel suggested that one aspect of particular relevance should be to look at whether a study involves subjects who have already failed on a checkpoint inhibitor, or those who have shown resistance to immuno-oncology in general. Signs of efficacy in these patients would clearly be of interest.

IO-IO or back to basics?

Paul Rennert, chief executive of Aleta Biotherapeutics, who was co-chairing the panel with Dr Mulé, drilled down into the changing expectations behind the various checkpoint combination approaches.

He admitted to having been one of the people who two or three years ago had made much of the potential of combining immuno-oncology with immuno-oncology, assuming that novel targets like Ox40, GITR, Tim3, Vista and others were going to raise immune responses strongly and usher in a new wave of post-PD-(L)1 agents.

"We thought we were going to get response rates up. We're not seeing that yet," he admitted. "Perhaps it's too early."

On the other hand, perhaps it is checkpoint inhibitor combinations with more traditional approaches, such as small molecules or even simple chemotherapy, that investors should pay attention to. The surge in chemo combo studies was another key finding of the *EP Vantage* report.

This issue could feed into other important areas such as pharmacoeconomics: a chemo combo approach would clearly be cheaper than one combining two IO agents.

At a separate Sachs Forum discussion focused on deal-making, Timothy Herpin, head of UK transactions at Astrazeneca, said there would likely be continued interest in non-IO mechanisms, but that these would play out in combination with an IO backbone.

Guillaume Vignin, head of IO licensing at Merck KGaA, said it was too early to call the non-IO combo approach a

trend. “But there are exciting data to be published,” he said. “The two will be working together – it will not all be about IO-IO.”

If one thing is certain, however, it is that data will come thick and fast, and this will affect the way deals are done. The important thing seems to be just to get deals signed to get the combos into the clinic, and generate data, as quickly as possible, said Mr Herpin.

“Once you have data we can work through the [deal] complexity,” he added.

A full version of *EP Vantage’s* report can be downloaded here.

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