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Asco interview – Glaxo steps out of the CAR for a multiple myeloma search

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Glaxosmithkline explains why it is eschewing CAR-T therapies in favour of antibody conjugates.

CAR-T has taken the oncology sector by storm, with big pharma and major biotechs having invested in a technology that has shown some impressive benefits in haematological cancer patients with few options. There are notable absences, including Glaxosmithkline – but the company still hopes to be a player in these diseases and is going up against CAR-T therapies with its BCMA-targeting antibody-drug conjugate GSK2857916.

While broadly complimentary of CAR-T, Glaxo's oncology chief, Axel Hoos, believes the group's ADC has advantages. He points to the ability to scale up a biological for commercial sale and deliver a therapy to patients without the complex manufacturing and treatment regimens required of CAR-T products like Kymriah and Yescarta. "It's a Lamborghini. Not everybody can afford a Lamborghini," he says of CAR-T.

"We made a conscious choice at some point to pursue an ADC over CAR-T. We just thought ADC was a faster way to the target," he adds.

Expanding

CAR-T makers are looking to break into the relatively large multiple myeloma space, having already carved a niche in late-line lymphoma and leukaemia. The BCMA-targeting mechanism being tested here was unlikely to escape notice from drug developers looking for the simpler approach of an antibody, and this is where Glaxo, Astrazeneca and Regeneron, to name three, come in.

GSK2857916 was little-noticed until it gained breakthrough therapy designation from the US FDA last November and positive data were presented at Ash a month later. *EvaluatePharma*'s consensus of sellside analysts now puts 2024 sales at $1.4bn, making it both Glaxo's biggest pipeline prospect and the biggest forecast seller of any pipeline project targeting BCMA.

It differs from the other top contenders in this class, which all seek to use the ubiquity of B cell maturation antigen on malignant plasma cells to deliver a neutralising immune response. Celgene is heavily invested in CAR-T, both licensing Bluebird Bio's bb2121 and owning Juno's JCARH125, but it is not alone. Novartis outlined data on its candidate at Ash, and Johnson & Johnson recently announced the start of a phase Ib/II programme for JNJ-68284528, which emerged from a partnership with Nanjing Legend and is based on the latter's LCAR-B38M.

“With time, as CAR-Ts get cheaper in terms of cost of goods, get more scalable and have more durability, and when we engineer the next generation of cells, they will become more competitive,” Mr Hoos says. “Today an antibody is easier to scale, easier to develop, easier to market and will likely win when you make a comparison with a CAR-T.”

He believes that all the drawbacks of the first generation of CAR-Ts – manufacturing failures and the vein-to-vein time that means some patients progress while waiting for the autologous therapies to be manufactured – will diminish over time as the sector grows experienced.

Response vs speed

That does not mean that Glaxo cannot learn from the progress of Bluebird, Celgene and others. Mr Hoos points out that if Bluebird’s pivotal trial is enrolling quickly it would be a sign that their manufacturing can meet demand. However, updated efficacy results also provide Glaxo with a target to match.

Comparing the leading BCMA-targeting agents in multiple myeloma		
	bb2121 (Asco)*	**GSK2857916 (Ash 2017)**
Objective response rate	96%	60%
Progression free survival	11.8 months	7.9 months
Duration of response	10.8 months	Not reached
**Patients receiving at least 150 million cells.*		

Bluebird’s bb2121 Asco data set showed an impressive 96% objective response rate (ORR) in patients who received a minimum of 150 million cells, progression free survival (PFS) of 11.8 months and a 10.8 month duration of response. That came at a cost of a frequent adverse events, including 63% having cytokine release syndrome and 33% neurotoxicity. Still, as specialists become more experienced with CAR-T they ought to be able to manage those side effects more effectively.

GSK2857916 has yielded a lower response rate – 60% in phase I, with 7.9 months median PFS and median duration of response that had not been reached as of its Ash readout.

Its side-effects tend to relate to the eyes, consisting of blurred vision, light sensitivity and dry eye – Bluebird has been eager to highight these. Bluebird has also pointed out that CAR-T toxicity occurs only when the one-time product is infused, rather than recurring with each dose (*Asco 2018 – Good might not be good enough for Bluebird, June 2, 2018*).

Mr Hoos acknowledges bb2121’s positive results. “Higher response rates, the durability is still a little bit unclear, and still some toxicities that come with CAR-T that are unique and different than what you get with an antibody. It looks a little bit better than it looked last time, but still not a change in perspective on CAR-T.”

Both Glaxo and Bluebird are looking towards their pivotal trials and of course the challenge of climbing up through the lines of care as Darzalex now has – so far, both only have results in heavily pre-treated patients. Mr Hoos says Glaxo has written the protocol for the first pivotal trial and is awaiting the first enrolment in order to make an announcement. This will happen “imminently”.

“Our expectation is that we will launch this in 2020 on the basis of data that reads out in late 2019,” he says.

Selected BCMA-targeting agents in clinical development for multiple myeloma								
		Global sales forecast ($m)						
Project	**Company**	**2019e**	**2020e**	**2021e**	**2022e**	**2023e**	**2024e**	**Phase**
GSK2857916	Glaxosmithkline	18	160	396	652	1,016	1,378	Phase II
bb2121	Celgene	-	108	163	274	390	498	Phase III
bb2121	Bluebird Bio	-	40	104	148	189	263	Phase III
JCARH125	Celgene	-	-	8	44	103	147	Phase II
Source: EvaluatePharma.								

On a parallel track the UK-based big pharma will begin testing in combination with standard of care – Revlimid or Velcade and dexamethasone – and immunotherapy combinations. These will start as phase II, and pivotal

trials could begin in 2019.

If Glaxo manages to get GSK2857916 to market in 2020 this would mark the company's first cancer drug launch since Mekinist and Tafinlar in 2013 – which were themselves part of the group's sale of marketed oncology products to Novartis just one year later.

Mr Hoos sees it as a fresh start. "We have not exited oncology. Oncology is back at GSK," he says. If GSK2857916 lives up to its now very high expectations, this might not be far off the mark.

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