Evaluate Vantage

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Ash 2018 – Legend’s mystery CAR raises more questions

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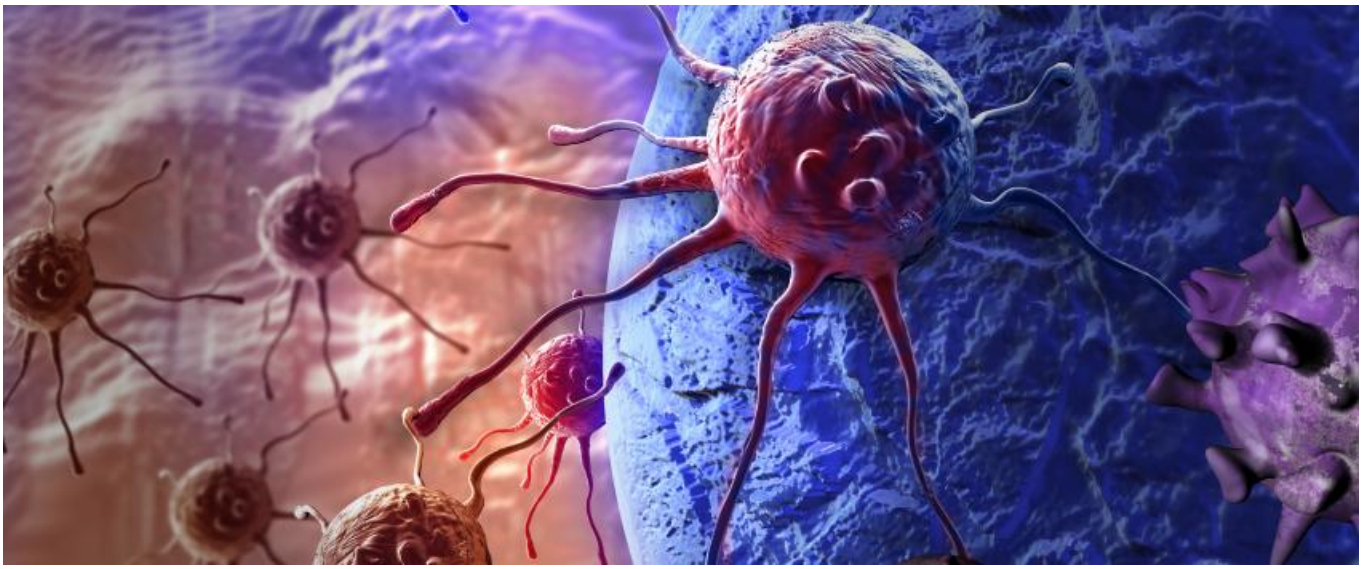

Nanjing Legend reveals continuing strong responses with its anti-BCMA CAR-T therapy in multiple myeloma, but relapses, a death and missing patients cloud the results.

Having suffered an attack from a mystery short seller, but with a $350m Johnson & Johnson deal under its belt, Nanjing Legend came into Ash with an air of expectation. Barring a low-key update a year ago this would be the first presentation of results from its China study of the CAR-T therapy LCAR-B38M since Asco 2017.

In the event the data, presented today, raised more questions than answers, not helped by the fact that the presenter’s poor English made answering delegates’ questions virtually impossible. Worst of all, however, was the glaring fact that the presentation did not include 23% of the patients treated in this multiple myeloma trial.

Such holes do little for the credibility of an asset that has been shrouded in mystery. J&J struck its deal with Nanjing, a subsidiary of the listed Chinese contract researcher Genscript Biotech, a year ago, handing across $350m up front.

It was not long ago that it became apparent that LCAR-B38M, a bispecific CAR, targets two separate BCMA epitopes, but it was not clear whether it was the same construct that J&J has taken into a US trial under the lab code JNJ-68284528.

J&J told *Vantage* that JNJ-68284528 used the identical bispecific construct as LCAR-B38M, but with modified manufacturing and scale-up processes.

Allegations

Trading in Genscript was briefly halted in September when an organisation calling itself Flaming Research made numerous allegations against Nanjing’s handling of the LCAR-B38M trial. These were swiftly rebutted in a detailed investor announcement.

However, the concern that the data are being parsed selectively has not entirely been allayed. The Ash update, like the Asco 2017 presentation, related to only one institution – the Second Affiliated Hospital of Xi'an Jiaotong University, in which 57 subjects have been treated.

Three other hospitals are taking part in the trial: Ruijin Hospital, Jiangsu Provincial and Shanghai Changzheng.

But these centres have only ever featured at a low-key update at Ash 2017, detailing eight complete and three partial remissions among 11 patients treated in these three sites by that time.

The September rebuttal to Flaming Research stated that Nanjing had in fact dosed a total of 74 subjects with LCAR-B38M, and Nanjing today said the outstanding six fell to the three other centres. J&J said study sites maintained independent responsibility for publishing data, and results from other centres would be presented in the future.

Nanjing Legend's developing LCAR-B38M dataset (NCT03090659)					
Presented at	Asco 2017	Ash 2017			Ash 2018
Data cut	Feb 2017	Aug 2017			Jun 2018
Patient n	35	11			57
Hospital (n)	Xi'an Jiaotong (35)	RM (6)	RJ (3)	CZ (2)	Xi'an Jiaotong (57)
Best ORR	100%	100%			88%
CR	15 (43%)	5 (83%)	2 (67%)	1 (50%)	42 (74%)
PR	20	1	1	1	8
No response	0	0	0	0	7
Notes	2 relapses	Further 6 pts treated			14 relapses
RM=Renji Hosp; RJ=Jiangsu Provincial Hosp; CZ=Shanghai Changzheng Hosp.					

While the best responses among the 57 Jiaotong University subjects look impressive, the data are flattered by the fact that these patients were less sick relative to studies of rival BCMA CARs.

Nanjing also revealed one death, from dyspnoea in the setting of grade 2 cytokine release, that seemed to be LCAR-B38M related. Also, 14 of the 50 responders had relapsed as at the June data cut.

J&J has yet to reveal any clinical data with JNJ-68284528.

A separate issue for the companies is how crowded the field of BCMA-targeting therapies has become (*Ash 2018 – The balancing act behind Bluebird's Goldilocks CAR, December 2, 2018*).

Several other assets with this mechanism put up impressive remission numbers, including a 100% overall response rate in a first-in-human trial of Celgene's FCARH143 in patients who had failed a median 11 prior therapies; there have been two BCMA-negative relapses in this trial.

Dr Damian Green of the Fred Hutchinson Cancer Center said his group was working on giving patients a gamma-secretase inhibitor to increase BCMA density and improve FCAR143's efficacy. However, of the BCMA assets Celgene got through its Juno takeover the commercial focus is on JCARH125, a trial of which saw one death from infection after grade 4 cytokine release.

Selected anti-BCMA CAR-T therapies					
Project	**Company**	**Preconditioning**	**Prior therapies**	**Data**	**Trial ID**
bb2121	Bluebird/Celgene	Cy/flu	7	n=39, ORR 77%, CR 31%	NCT02658929
bb21217	Bluebird/Celgene	Cy/flu	7	n=12, ORR 83%, CR 25%*	NCT03274219
LCAR-B38M	Nanjing Legend/J&J	Cy	3	n=57, ORR 88%, CR 74%**	NCT03090659
CART-BCMA	Novartis/Penn	None -> cy	7	n=25, ORR 48%, CR 8%	NCT02546167
JCARH125	Celgene	Cy/flu	7	n=44, ORR 82%, CR 27%***	NCT03430011
MCARH171	Celgene/MSKCC	Cy or cy/flu	6	n=11, ORR 64%, CR 0%	NCT03070327
FCARH143	Celgene/Fred Hutch	Cy/flu	11	n=11, ORR 100%, CR 36%	NCT03338972
P-BCMA-101	Poseida	Cy/flu	6	n=19, ORR 63%, CR 5%****	NCT03288493
ALLO-715	Allogene/Cellectis	Campath or ALLO-647	Phase I trial planned for 2019		
**Lowest dose only; **1 of 4 centres only; ***77% got bridging chemo; ****no requirement for BCMA expression.*					

Away from the frenzy of BCMA-targeting CARs, bispecifics and conjugates one early-stage multiple myeloma asset stood out. Celgene's MCARH109, the result of Juno's deal with Eureka, should be in the clinic next year; this CAR hits a novel target, GPRC5D, and the study will include subjects previously treated with anti-BCMAs, Memorial Sloan Kettering's Dr Eric Smith told Ash.

Perhaps the greatest surprise, however, came from Poseida, which has a J&J CAR-T alliance but is developing P-BCMA-101 on its own. Its Ash presentation stated that this project would be filed for approval in 2020; this suddenly puts P-BCMA-101 on the same ambitious timeframe as Bluebird/Celgene's sector-leading bb2121.

This story has been updated to incorporate subsequent replies from J&J.