Evaluate Vantage

September 12, 2018

The first real challenge to multiple myeloma CAR-T therapy

Jacob Plieth

Amgen’s AMG 420 yielded early but spectacular remissions, leaving Boehringer Ingelheim with egg on its face.

Surprise disclosure of the results from five multiple myeloma subjects given Amgen’s anti-BCMA bispecific AMG 420 on Sunday emerged as the first real threat to Bluebird Bio’s similarly acting CAR-T therapies bb2121 and bb21217.

Until now only CAR-T was thought capable of delivering these kinds of remissions, and bb2121 at present offers the most impressive example. Perhaps this explains why Boehringer Ingelheim gave up rights to AMG 420 just two years ago, despite trumpeting a push into oncology (*Behold the son of Blincyto, September 2, 2016*).

Numerous approaches have been taken to hitting the BCMA antigen, but the analogy in childhood leukaemia of targeting CD19 using Amgen’s Blincyto or Novartis’s Kymriah suggested that a bispecific’s efficacy could never match that of adoptive cell therapy.

This is why the AMG 420 data are spectacular: all five subjects treated at the highest dose reported complete responses, with four going minimum residual disease-negative and four still being in remission at up to 10 months, the Myeloma 2018 conference in San Diego heard.

The patients had had four to six prior lines of therapy, and four had had two or three stem cell transplants. Bluebird’s most recent bb2121 data cut, also in a heavily pretreated cohort, showed an 81-100% objective response rate, depending on the number of CAR-T cells infused.

BCMA-targeting approaches in clinical trials			
Project	**Approach**	**Company**	**Trial ID**
Phase III			
bb2121	CAR-T	Celgene/Bluebird	NCT03651128
Phase II			
GSK2857916	ADC	Glaxosmithkline/Seattle Genetics	NCT03525678
JCARH125	CAR-T	Celgene (ex Juno)	NCT03430011
Phase I			
AMG 224	ADC	Amgen	NCT02561962
MEDI2228	ADC	Astrazeneca	NCT03489525
SEA-BCMA	ADC	Seattle Genetics	NCT03582033
CC-93269	Bispecific MAb	Celgene	NCT03486067
AMG 701	Bispecific MAb	Amgen	NCT03287908
JNJ-7957	Bispecific MAb	Johnson & Johnson/Genmab	NCT03145181
PF-06863135	Bispecific MAb	Pfizer	NCT03269136
AMG 420	Bispecific MAb	Amgen (ex Micromet/Boehringer)	NCT02514239
bb21217	CAR-T	Celgene/Bluebird	NCT03274219
KITE-585	CAR-T	Gilead (ex Kite)	NCT03318861
CAR-BCMA-T cell	CAR-T	Carsgen Therapeutics	NCT03380039
MTV273	CAR-T	Novartis	NCT02546167
AUTO2	CAR-T	Autolus	NCT03287804
JNJ-68284528	CAR-T	Johnson & Johnson/Nanjing Legend	NCT03548207
P-BCMA-101	CAR-T	Poseida Therapeutics	NCT03288493
Source: EvaluatePharma & clinicaltrials.gov.			

AMG 420's history is intriguing; like Blincyto the asset had been originated by Micromet, the biotech group acquired by Amgen for $1.6bn in 2012.

Boehringer had been Micromet's partner on AMG 420, or BI 836909, as it was then called, but sold its remaining interest to Amgen for an undisclosed amount. With hindsight this seems strange, and presumably reflects a lukewarm attitude at the German group to either the BCMA antigen or bispecifics in general.

Boehringer told *Vantage* that its focus was on "treatments with breakthrough potential in lung and gastrointestinal cancers. This is why we are very satisfied that Amgen is further advancing [AMG 420]".

Though bispecifics have yet to shake up the markets, the threat they pose to cell therapy is real: owing to convenience, and presumably a lower cost, a bispecific would naturally be given before CAR-T, and a patient reporting an antigen-negative relapse on the former would logically no longer be a candidate for the latter, if the same antigen is targeted.

Further data from the AMG 420 trial are now one of the hottest tickets of December's Ash meeting.

This article has been updated to add commentary from Boehringer.