Evaluate Vantage

August 24, 2021

New fault lines emerge in Car-T therapy

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In second-line lymphoma – a setting where Breyanzi and Yescarta have already succeeded – Kymriah fails to beat stem cell transplant.

For Car-T therapy to become anything other than a niche hospital procedure it has to move into early treatment lines. Novartis's Kymriah seems unlikely to secure such an accolade, however, having today failed to beat autologous stem cell transplantation in a second-line lymphoma study.

For the Swiss group this is especially galling as Kymriah's two big competitors, Bristol Myers Squibb's Breyanzi and Gilead's Yescarta, have just succeeded in similar trials. Still, it will be important to bear in mind trial design differences, though one take is that important fault lines are emerging between CD19-directed Car-T therapies.

On a cross-study basis this was already becoming apparent in these treatments' approved salvage uses in second-line or later lymphoma, where for instance Yescarta and Breyanzi boast overall remission rates above 70% while Kymriah's is 50%, according to US prescribing information.

Second line

Now the battle lines move to second-line lymphoma, an important setting where patients have relapsed after or are refractory to front-line Rituxan plus chemo.

Belinda, the trial Novartis today said had failed, compared giving these patients Kymriah head to head against the standard of care of chemo followed, in responders, by autologous transplant. Novartis said Belinda's primary endpoint, event-free survival (EFS), failed to show a benefit for Kymriah.

An important point is that Belinda allowed the option of platinum-based immunochemotherapy before dosing Kymriah or the standard of care, a fact that might have rendered any subsequent benefit statistically insignificant.

Bristol's corresponding Transform and Gilead's Zuma-7 studies had similar designs and also tested EFS as primary endpoint, though they did not have the immunochemotherapy option. On June 10 Bristol said Breyanzi had beaten chemo plus transplant in terms of EFS, as well as in terms of complete response rates.

Two weeks later Yescarta scored in Zuma-7, with Gilead quantifying the EFS benefit versus chemo and transplant as a 60% reduction in event risk ($p<0.0001$). There was also a benefit in overall remission rate; overall survival was insufficiently mature for Transform and Zuma-7 alike.

Car-T therapy in 2nd-line lymphoma				
			Result	
Product (company)	**Trial**	**Population***	**Primary endpoint**	**Secondary endpoint(s)**
Breyanzi (Bristol Myers Squibb)	Transform	175 aggressive BCL patients	Positive for EFS	Positive for CR & PFS; OS immature
Yescarta (Gilead)	Zuma-7	359 DLBCL patients	Positive for EFS (HR 0.398, p <0.0001)	Positive for ORR; OS immature
Kymriah (Novartis)	Belinda**	355 aggressive BCL patients	Negative for EFS	No info

*Note: *all 2nd line after Rituxan + chemo, compared against standard of care/autologous transplant in responders; **included the option of platinum immunochemotherapy before Kymriah or SoC. BCL=B-cell lymphoma; DLBCL=diffuse large B-cell lymphoma. Source: company statements.*

Next it will be time to pick apart the data, with a clear focus falling on the possible effect of Belinda's addition of platinum immunochemotherapy.

In terms of disease criteria, Zuma-7 enrolled only diffuse large B-cell lymphoma patients, while Transform and Belinda both specified aggressive B-cell lymphoma but allowed subjects with grade 3B follicular lymphoma, a less aggressive type.

The precise balance of baseline characteristics will be scrutinised to see whether the studies offer an apples-to-apples comparison. A similar thing goes for subsequent therapy. How many patients in each study's control cohorts went on to receive Car-T, and did this influence outcomes? How durable are responses and what will the gold standard of median overall survival tell us once it is reached?

Some answers should be forthcoming when full data from these recent interim analyses are presented, perhaps at December's Ash meeting. In the meantime doctors and analysts alike will digest the emerging data suggesting that Kymriah, the first Car-T therapy to make it to market, might not be the best.

Car-T data in ≥2nd-line lymphoma					
Product (company)	**Trial**	**ORR**	**CR**	**mDoR**	**2026e sales ($m, all indications)**
Breyanzi (Bristol Myers Squibb)	Transcend	141/192 (73%)	104	16.7mth	1,266
Yescarta (Gilead)	Zuma-1	73/101 (72%)	52	9.2mth	1,234
Kymriah (Novartis)	Juliet	34/68 (50%)	22	NE	1,214

Note: ORR=overall remission rate; CR=complete responses; mDoR=median duration of response; NE=not estimable. Source: product labels & Evaluate Pharma sellside consensus.