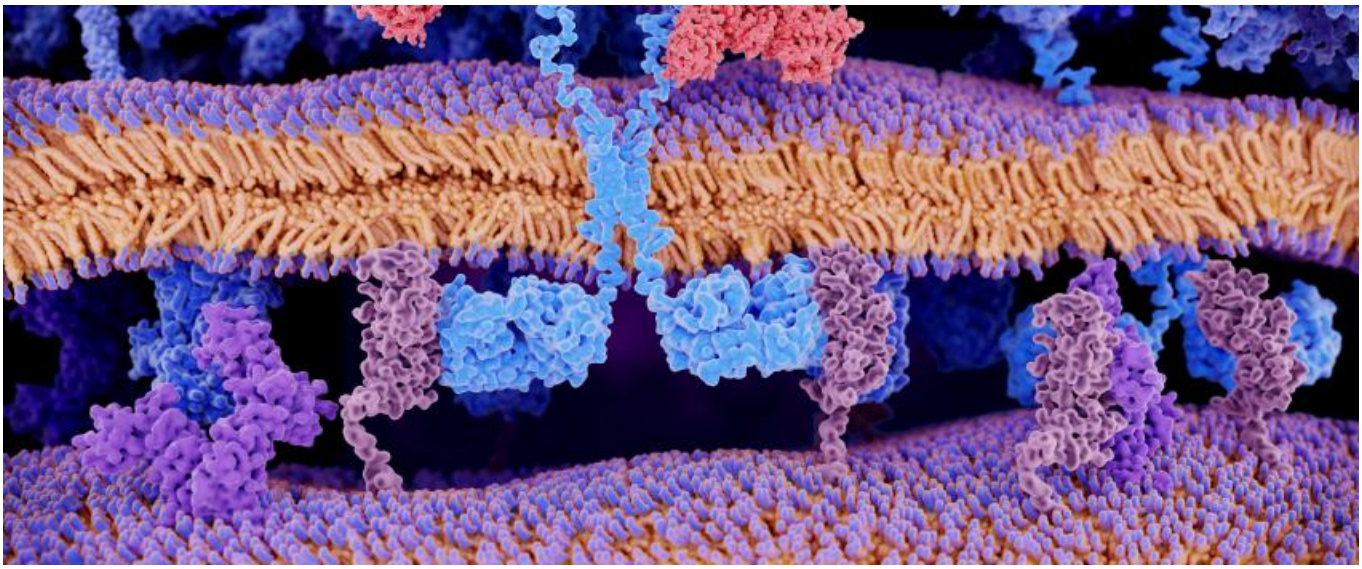
Evaluate Vantage

December 14, 2021

Ash 2021 – why Breyanzi and Yescarta might refresh the parts Kymriah cannot reach

Jacob Plieth



Novartis will not pursue Kymriah's use in second-line lymphoma; but have Breyanzi and Yescarta proved enough to be filed in this setting?

With Gilead's Yescarta and Bristol Myers Squibb's Breyanzi showing that Car-T might replace stem cell transplant in second-line lymphoma, one question is why Novartis's Kymriah failed in precisely this setting. Today's Ash late-breaking presentation provided some clues.

Excuses notwithstanding, the bottom line is that Novartis will not file Kymriah for this early use, the Swiss firm confirmed to *Evaluate Vantage*. A bigger question is whether the strong event-free survival benefit shown in Yescarta and Breyanzi's corresponding successful trials is enough to see these two competitors filed and approved for use in the second-line setting.

Presentation at Ash of detailed data from all three studies in question, Breyanzi's Transform, Yescarta's Zuma-7, and Kymriah's Belinda, has made the possibility of Car-T replacing second-line stem cell transplantation in lymphoma one of the biggest topics of this year's meeting. Each trial compared Car-T against standard of care, meaning chemotherapy followed by transplant in patients who go into remission.

Crossover conundrum

But a key issue has emerged, in that a majority of patients in the control cohorts of these three trials crossed over to Car-T on disease progression – as part of protocol in Transform and Belinda, and off-protocol in Zuma-7. Thus the EFS metric loses importance if an absence of overall survival benefit suggests that patients relapsing on second-line standard of care can still be rescued by Car-T in its currently approved third-line setting.

The jury is still out on whether this is the case. Both the successful trials, Transform and Zuma-7, showed an immature OS analysis numerically favouring Breyanzi and Yescarta, the former with widening survival curves, admittedly from an interim analysis.

But Zuma-7's primary investigator, Dr Frederick Locke from Moffitt Cancer Center, told Sunday's Ash plenary session that treatment switching in the standard-of-care cohort was likely confounding a significant OS benefit.

However, for her part University of Colorado Cancer Center's Dr Manali Kamdar, who presented the Transform data on Saturday, said patients who got Breyanzi later (after crossing over from standard of care) did not do as well as those who got it earlier. This appears to back the importance of giving Breyanzi second rather than third line.

However this plays out, it will be up to regulators to determine whether the EFS benefits Bristol and Gilead have shown are enough to secure second-line approvals in the absence of a mature OS analysis. The EFS findings themselves show Yescarta and Breyanzi beating second-line standard of care by a huge margin, cutting risk of progression by over 60%.

Moderating a press briefing, Dr Laurie Sehn of University of British Columbia said it was “inevitable that [Car-T] will become the standard of care” in second-line lymphoma. Without being drawn on which therapy was better, she noted that the Zuma-7 data were very mature, while Transform’s was an interim analysis.

Car-T in 2nd-line lymphoma; a cross-trial comparison			
	Yescarta (Gilead)	**Breyanzi (BMS)**	**Kymriah (Novartis)**
Study	Zuma-7	Transform	Belinda
Baseline disease	Adults within 12mth of adequate 1st-line chemo and intended to proceed to stem cell transplant	Adults, incl with secondary CNS lymphoma, within 12mth of 1st-line therapy, eligible for stem cell transplant	Adults within 12mth of 1st-line chemo
Active bridging?	Optional bridging with steroids (no chemo)	63% got chemo bridging	83% got chemo bridging
Active n	180 (of which 10 not infused)	92 (of which 2 not infused)	162 (of which 6 not infused)
Control arm	Chemo, then stem cell transplant in responders (36% transplanted)	3 chemo cycles, then BEAM + stem cell transplant in responders (47% transplanted)	Chemo, then stem cell transplant in responders (33% transplanted)
Control n	179	92	160
Control crossover?	Yes, off protocol 100 (56%) patients who failed SoC got commercial/investigational Car-T	Yes, 50 (54%) SoC pts not responding crossed over to Breyanzi	Yes, 81 (51%) crossed over to Kymriah; 72 crossover pts were evaluable, and yielded ORR of 40%
EFS	Median 8.3mth vs 2.0mth (HR=0.398; p<0.0001)	Median 10.1mth vs 2.3mth (HR=0.349; P<0.0001)	Median 3.0mth vs 3.0mth (HR=1.07; p=0.69)
OS (immature)	Median NR vs 35.1mth (HR=0.73; p=0.027)	NR vs 16.4mth (HR=0.51; p=0.0257)	16.9mth vs 15.3mth (HR not disclosed, but likely >1.00)
Grade ≥3 CRS	6%	1%	5%
Grade ≥3 neurotox	21%	4%	3%
Source: Ash.			

Belinda’s bust

One Car-T therapy that will not be moving up is Novartis’s Kymriah, whose Belinda study was already known to be a bust. Some blame for this has been placed on the fact patients given Kymriah were more sick than those in the control cohort.

But speaking to *Vantage* Stefan Hendriks, Novartis’s head of cell and gene, also said time from randomisation to infusion was longer in Belinda than in the other two trials. This has been an ongoing problem for Novartis, and while it was partly down to Covid-19 and capacity constraints the upshot is that some patients did not get Kymriah in time, and saw their disease get worse.

Investigators said time from leukapheresis to infusion of Car-T cells, including lymphodepletion, was on average 52 days in Belinda, versus just 29 in Zuma-7.

Another quirk was that Novartis capped EFS assessment at 12 weeks. Some patients – Mr Hendriks did not say how many – responded to Kymriah after this point, but because they had stable or progressive disease at 12 weeks they were nevertheless counted as having evented.

Still, Mr Hendricks was clear: “Because of the outcome of [Belinda] we will not submit for a second-line

indication.” But he said a pivotal second-line lymphoma trial would be carried out with YTB323, a next-generation Car-T that can be manufactured within two days.

Breyanzi safer?

Over the weekend discussion turned to fault lines emerging between the two successful studies, Transform and Zuma-7. A key matter appears to be safety: while both trials saw a similar amount of severe all-cause treatment-related adverse events, severe cytokine release syndrome (CRS) and neurotoxicity was lower in Transform than in Zuma-7.

Dr Kamdar said this made Breyanzi “appealing not just from a standpoint of efficacy but also [from its] extremely tolerable safety”. Only one Breyanzi patient had grade 3 CRS, and there was no grade 4 or 5 CRS or neurotoxicity. There was one Car-T treatment-related death in each of the two studies.

Other differences were that Transform allowed patients with a broader histology profile than Zuma-7, and it did, like Belinda, allow bridging chemo while the Car-T cells were being produced. Zuma-7 allowed steroids during this phase, but, crucially, not chemo.

In a cutting remark, Dr Locke stated: “We wanted to know: could [Yescarta] be given without the confounding effect of chemotherapy, which we know can cause a response?”

One remaining problem is what to do once a second-line lymphoma patient on Car-T does relapse. Both presenters said there was no appropriate standard of care here, but said a small number of such relapsing patients in both studies ended up getting transplanted; in Zuma-7 this amounted to 19 patients, nine of whom are still alive, said Dr Locke.

No matter, the argument shifts to whether, given Car-T’s better efficacy, payers should shell out for this rather than stem cell transplant. Dr Kamdar said it was too early to talk of financial toxicity, but stressed Car-T’s potential as a “once and done therapy”. Dr Locke said some of the intensive hospital care costs were similar in transplantation and Car-T.

The efficacy data seem pretty clear, so the ball now enters the court of the FDA on whether to approve, and of payers to decide whether to pay up.