Kite flies, but durability remains the key unknown

Long-awaited interim data from Kite’s Zuma-1 trial have shown what on the face of it looks to be an approvable level of responses. How many of these are durable beyond three months remains the study’s most important unknown.

This was always going to be the case, and to smart investors Kite’s ability to file KTE-C19 this year on the basis of three-month data was in doubt even before the Zuma-1 results were unveiled yesterday. The doubts do not seem to have troubled a largely ecstatic sellside, which helped send Kite stock up 12% in early trade today.

Probably the wildest sentiment was expressed by Maxim’s Jason McCarthy, who on a call yesterday congratulated Kite for looking like it “may have won the CAR-T race”. Suntrust was more circumspect, quietly opining this morning that KTE-C19 would not be filed until mid-2017; Kite has been gunning for a submission by the end of 2016.

This is not to say that there is nothing optimistic in Zuma-1: CAR-T product was successfully manufactured in 99% of patients, and none went on to receive a stem cell transplant. Manufacturing failures have plagued academic trials, while the suggestion that CAR-T serves merely as a bridge to transplant is a damper on sentiment.

But right now Kite has only three months’ data to take to the FDA (Event – Kite shoots, but what’s the target?, September 20, 2016). In the 51-patient diffuse large B-cell lymphoma (DLBCL) subset this stands at a 39% overall response rate, with 33% complete remissions.

This is in line with analysts’ recently scaled back expectations, but the trouble lies in the comparison with responses seen shortly after the CAR-T project was dosed, when 76% of patients were responding, with a 47% CR rate. This means that over the following couple of months up to half the patients relapsed, and additional relapses, if now seen, could be disastrous.

The relapse question in Kite’s Zuma-1 trial

<table>
<thead>
<tr>
<th></th>
<th>Phase I (n=7)</th>
<th>Phase II (n=51)*</th>
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<tbody>
<tr>
<td><strong>Data cut</strong></td>
<td>ORR</td>
<td>CR</td>
</tr>
<tr>
<td>30 days</td>
<td>71%</td>
<td>57%</td>
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<tr>
<td>3 months</td>
<td>43%</td>
<td>43%</td>
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<tr>
<td>6 months</td>
<td>43%</td>
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<td>9 months</td>
<td>43%</td>
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*complete DLBCL cohort only.

The hope is that the initially relapsing patients were just pseudo-responders, and that three-month remissions will be durable in the longer term. Kite argues that this is what happened in Zuma-1’s phase I portion where, after a third of initial responders relapsed, a 43% three-month CR rate was maintained into months six and nine.

Bullish analysts at Stifel called the latest three-month CR rate “durable”; whether the FDA agrees is less certain. Kite also moved the goalposts slightly in revealing preliminary results in a broader subset of lymphoma patients, flattering the ORR and CR data slightly, though strictly the interim Zuma-1 analysis related to DLBCL.

There are few like-for-like comparators: the Scholar-1 relapsed lymphoma meta-analysis that Kite sets as its
benchmark - 26% ORR, 8% CRR - relates to long-term outcomes, while Juno's recent trial of JCAR014 - showing 72% ORR and 50% CR - has very short follow-up.

Two deaths

Still, the problem of side effects refuses to go away: Kite said two Zuma-1 patients died owing to cytokine release syndrome - a toxicity that most groups are claiming is controllable.

Kite would not commit as to whether the interim result was enough for a KTE-C19 filing by the year end, only saying it would now discuss the "very compelling" dataset with the agency.

It also appeared to dispel the chances of further Zuma-1 data emerging soon. Full results presentation - presumably at ASH in December - will relate only to the three-month cut, and with the DLBCL cohort not completing six months' follow-up until January 7 it seems that the FDA will have little more to go on.

If filing is delayed, or the agency decides to wait for more data, Kite's CAR-T lead over Juno and Novartis, which have had slippages of their own, will have narrowed. December’s data presentation should elucidate patients’ baseline characteristics and any correlation between toxicity and response, and will again confirm ASH as one of the year’s most important scientific conferences.

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