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TG pulls victory from the jaws of defeat

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The Unity-CLL trial shows ublituximab plus umbralisib conferring an unexpected progression-free survival benefit.

With TG Therapeutics yesterday claiming victory in the Unity-CLL trial, the study's standing among biotech's most curious is confirmed. Unity-CLL had suffered numerous delays and had its focus changed after an initial failure, but despite all this it has apparently shown a strong progression-free survival benefit.

The result positions the combo TG tested, ublituximab plus umbralisib, to be filed by the end of 2020 for chronic lymphocytic leukaemia (CLL). The projects' sales will depend on the absolute benefit seen, the safety profile, and how strong the Unity-CLL result was in first-line versus relapsed/refractory subjects.

Investors seeking answers to these questions will need to wait until the full data are presented at a medical meeting – Ash in December looks a likely venue. Sellside consensus compiled by *EvaluatePharma* sees the two projects generating a combined $1.7bn of revenue in 2026, though this includes some $300m from ublituximab's separate potential use in multiple sclerosis.

High statistical significance

For now, however, TG can boast of a PFS benefit for its combo that beat the comparator cohort, Roche's Gazyva plus chlorambucil, with a high degree of statistical significance ($p<0.0001$).

Though the still undisclosed absolute result is key, TG closed up 34% yesterday, with a valuation of $1.8bn, and today took the opportunity to tap the market for $60m. TG separately hopes to complete a US lymphoma filing for umbralisib monotherapy by mid-2020.

For Unity-CLL, however, the biggest mystery remains why a study that had not shown a benefit in terms of objective response would nevertheless read out positively for PFS. If patients are progression-free it is logical to expect them to be responding, but the TG readout suggests no correlation between the two measures.

Nevertheless, Michael Weiss, TG's chief executive, insisted that the ORR analysis had not failed, but was insufficiently mature to be performed. "Even today we don't know if there is or is not an ORR benefit," he told *Evaluate Vantage*. "Not that it matters now."

He also said CLL was different from other cancers in that chemo tended to result in high responses but limted PFS. Indeed, in the relapsed CLL trial Ascend Astrazeneca's Calquence showed a strong PFS advantage over Rituxan plus Zydelig or bendamustine, but showed no ORR improvement.

Alethia Young, an analyst at Cantor Fitzgerald, said Unity-CLL had been powered to show a 40% improvement in PFS, and the goal was for the combo to reduce risk of progression by 29% (HR=0.71). Given that this was an interim result, causing Unity-CLL to be halted early for efficacy, the actual HR should be even better, “in the neighbourhood of 0.50”, wrote Ms Young yesterday.

A separate question is how ublituximab, an anti-CD20 antibody, and umbralisib, a PI3K delta inhibitor, will compete against new regimens such as Abbvie/Johnson & Johnson’s Imbruvica and Roche/Abbvie’s Venclexta. In first-line CLL Venclexta plus Gazyva cut risk of progression versus Gazyva plus chlorambucil by 67%, while Imbruvica beat chlorambucil alone with a staggering HR=0.16.

Importantly, Unity-CLL comprised first-line as well as relapsed/refractory subjects, in a ratio of 60/40. Though TG insists that the PFS benefit was observed across both populations, the precise contribution of each will be a key datapoint to watch, and should determine the drugs’ potential labels.

PI3K first

On an analyst call yesterday TG hailed its combo as being the first to show the benefit of a PI3K delta inhibitor in front-line CLL; this mechanism, courtesy of Gilead’s ill-fated Zydelig, has become associated with toxicity, and assuming that TG’s safety data hold up this could be a key selling point.

TG also said Unity-CLL was a springboard for additional combinations, and the company’s pipeline also includes a BTK inhibitor, TG-1701.

Still, investors would be right to remain cautious until the full data are disclosed. Unity-CLL’s inability to show a remission rate benefit scuppered TG’s accelerated approval plan, and prompted a change of focus to PFS. Then the PFS readout was delayed twice, forcing the company to add an interim analysis (*TG shrugs off another delay, but history is against it, March 4, 2020*).

It is with this analysis that TG has, at the eleventh hour, found something positive. Whether it has struck gold will only become clear once the full data are known.

This story has been updated to add comments from TG.