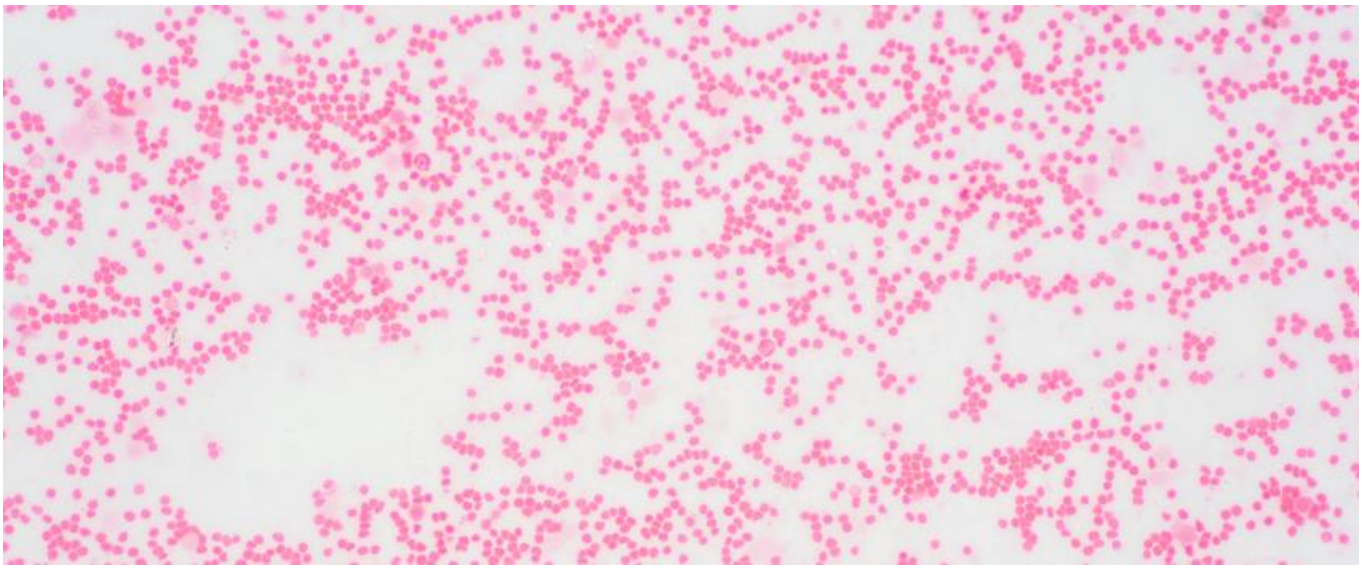
Evaluate Vantage

May 25, 2023

Asco 2023 – Commands leaves the door open for Geron

Jacob Plieth



Full data from Reblozyl's Commands study show limited activity in MDS patients without ringed sideroblasts – a boon for Geron.

The recently intensifying battle in myelodysplastic syndromes between Bristol Myers Squibb's Reblozyl and Geron's imetelstat appears to have turned in favour of the latter's underdog: presentation of the front-line Commands trial at Asco has confirmed Reblozyl's limited activity in patients without ringed sideroblasts.

A pre-Asco press briefing put a positive spin on the data, but the results speak for themselves. According to Commands' primary endpoint there was no benefit at all in ringed sideroblast-negative subjects, who comprise some two thirds of this MDS population. Crucially, Geron's Imerge trial did suggest that imetelstat was active in these patients.

There are further distinctions, most importantly that Commands is a first-line MDS trial, pitting Reblozyl against erythropoiesis-stimulating agents (ESAs), while Imerge tested imetelstat in patients progressed on or ineligible for ESAs.

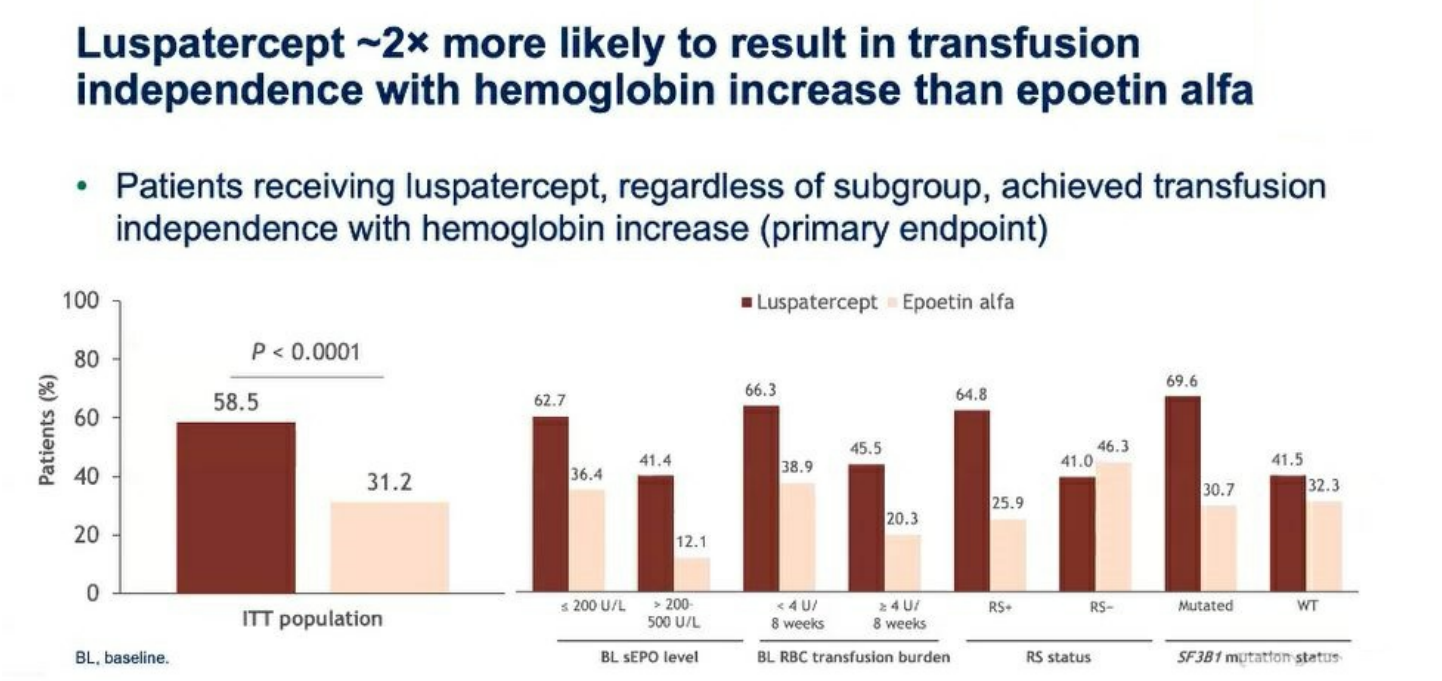
Reblozyl is already approved for post-ESA use in low-risk MDS, though only in ringed sideroblast (RS) positive patients – a fact that apparently does not preclude some off-label prescribing in RS-negative MDS. Full data from Imerge will be presented alongside the Commands results at an Asco session on 2 June.

Paradigm shift

Presenting data to the press this week Dr Guillermo Garcia-Manero, from the MD Anderson Cancer Center, called Commands a "paradigm shift in the treatment of low-risk MDS-associated anaemia", and a result thanks to which Reblozyl could replace ESAs as a new front-line option.

The basis for this enthusiasm was that Reblozyl was nearly twice as likely to result in transfusion independence with haemoglobin increase than epoetin alfa. 58.5% of Reblozyl recipients achieved this at 12 weeks, Commands' primary endpoint, versus 31.2% of patients given epoetin alfa ($p<0.0001$).

However, this all-comers effect was clearly driven by RS-positive patients. Those who were RS-negative derived no added benefit, with 12-week transfusion independence of 41.0% for Reblozyl versus 46.3% for epoetin alfa.



Source: Dr Guillermo Garcia-Manero & Asco.

Despite this, Garcia-Manero argued that Reblozyl should be used irrespective of RS status. Commands did not reflect the real-world population because over 60% of enrolled patients were RS-positive, and the trial was "not powered to see a big difference ... in the RS-negative context", he told the Asco press briefing.

Furthermore, he pointed to duration of transfusion independence, a secondary Commands endpoint that he suggested was as important as response itself. Here there was a strong numerical benefit favouring Reblozyl versus epoetin alfa among all-comer, RS-positive and RS-negative patients.

Commands prompt

The importance of Commands is twofold. Firstly it will likely result in Reblozyl getting a front-line label in low-risk MDS – though clearly how broad this is has yet to be determined. Secondly, depending on the extent to which the Bristol drug replaces front-line ESAs, it will change the second-line treatment landscape.

However, as long as Reblozyl is not indicated for RS-negative MDS the second-line imetelstat opportunity, which always looked likely to be limited to this population, should remain intact. Moreover, though the Geron project has not been tested in post-Reblozyl MDS, a recent KOL survey cited by B Riley analysts suggested that prescribers would use it in 55% of such patients.

Evaluate Pharma sellside consensus shows forecast 2028 revenues of $2.5bn for Reblozyl and $849m for imetelstat. Though each bank will make different assumptions about the chances of front-line use and/or an RS-agnostic label, if Reblozyl remains limited to RS-positives the peak sales forecasts could take a hit.

According to Garcia-Manero Reblozyl's response duration, relative safety and ease of SC administration every three weeks means that the drug "likely will become the standard of care for the majority of [low-risk] patients, regardless of whether they are RS-positive or negative". Whether this in fact happens depends on prescribers and the FDA.