Evaluate Vantage

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ASH – Interesting theories, but doubts on novel myelofibrosis projects remain

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Across the myelofibrosis landscape, seeing Jakafi's failure to live up to expectations, Sanofi's discontinuation of fedratinib and an uptick in industry focus on other mechanisms of action, you would be forgiven for thinking that the wind was fast going out of JAK inhibitors.

On the other hand, non-JAK approaches are hardly storming through studies with flying colours. Among ASH presentations affecting small-cap biotechs, one of the most closely watched was an update from a maverick physician on Geron's telomerase inhibitor imetelstat. Initial efficacy was confirmed, but safety ultimately failed to convince.

The physician in question, the Mayo Clinic's Dr Ayalew Tefferi, is a myeloproliferative disorders expert who had led an open-label, 33-patient myelofibrosis study of imetelstat. Release of the ASH abstract had earlier caused Geron's stock to surge on what was hailed as unprecedented efficacy: four complete remissions and one partial remission.

But doubts soon set in, mainly centring on a new definition of remission in terms of disease signs like normalisation of platelet count and extent of bone marrow fibrosis, rather than symptoms like reduction in spleen size. The new criteria – drafted by Dr Tefferi himself – only came into effect this year.

"The drug works"

Still, in Monday's presentation of fuller data at ASH Dr Tefferi did not hold back, saying imetelstat "clearly shows antimyeloproliferative activity ... the drug works".

He called the 23% rate of remission (five of 22 evaluable patients) something "never seen before" – hardly surprising given that this was the first time the new criteria had been utilised. There has not been a single relapse among the responders, he said, but would not be drawn on the correlation between bone marrow fibrosis and spleen size.

More flesh was put on the bones later in the day when Geron presented its own analysis of Dr Tefferi's data, as the company put it, to make it compliant with regulatory fair disclosure. The message was that, indeed, Geron broadly agreed with Dr Tefferi.

The company's analysis "certainly suggests disease-modifying activity", said its chief executive, John Scarlett. But it was clear that imetelstat's safety would continue to be a concern; an intensive-dosing arm had to be switched to milder dosing after severe myelosuppression was seen in patients.

Moreover, Geron revealed that two deaths had taken place, one of which was "possibly related" to imetelstat. However, the company put this down to a controversial decision to enrol into the aggressive dosing arm this very ill patient, who ultimately suffered prolonged myelosuppression.

On the other hand, one of the 22 patients had had a severely enlarged spleen that did shrink after treatment – and after this patient survived myelosuppression – Geron said. The suggestion is that, if patients can survive imetelstat's toxicity, the project could have a future.

Interestingly, the company attempted to put clear blue water between itself and Dr Tefferi, saying the physician was "his own man", and that it did not hold with all his views. Dr Tefferi had made a comment in his earlier presentation suggesting that this feeling was mutual.

For now, Geron plans to begin a company-sponsored myelofibrosis study next year. It reported third-quarter cash of $66m, and if a fund-raising is on the cards this will not have been helped by the stock coming off 7% on Tuesday.

Tefferi's sweet revenge

Telomerase upregulation is linked to tumour regenesis and myeloproliferative neoplasms, and imetelstat is thus a myelofibrosis project that uses pathways other than inhibition of JAK. Other non-JAKs – including thalidomide analogues like Celgene's lenalidomide and pomalidomide – have also progressed slowly.

In a separate ASH session Dr Tefferi presented a post mortem of pomalidomide's phase III myelofibrosis study, which had held much promise owing to its primary endpoint – patients reaching transfusion independence – but which in the event proved an almost total failure, with response rates of 16% in active and placebo cohorts, and a dismal p value of 1.00.

Although Dr Tefferi said there was no way to spin this into anything other than a negative result, he did point to the secondary endpoint of platelet response, where rates clearly favoured pomalidomide (p=0.006). He said pomalidomide might benefit some anaemic patients, but that he was "unable to prove this under the (study's) current design".

He speculated that patients most likely to respond should have been recruited, "as I had suggested before I was overruled". As if to live up to his controversial reputation, he thus described the study's failure as "sweet revenge".

Another way

Despite the setbacks the industry looks set to explore alternative pathways, if for no other reason than because some 40% of myelofibrosis patients appear to be negative for the JAK2V617F mutation, suggesting other mechanisms in play.

Speaking at an ASH educational session on Saturday, the University of Chicago's Dr Olatoyosi Odenike cited approaches including

established drugs like azacitidine, HDAC inhibitors like Novartis's panobinostat and Italfarmaco's givinostat, Hsp90 inhibitors, and Gilead's novel LOXL2 MAb simtuzumab.

She also suggested that there was mileage in "relevant combinations" to optimise activity, citing a trial testing Jakafi combined with Novartis's Hedgehog pathway inhibitor LDE225.

For its part, Geron said it was too early to speculate on combination therapies, and too early to say where imetelstat might fit into the myelofibrosis treatment paradigm.

Selected myelofibrosis projects

Project	Company	Study	Trial ID
Pomalidomide	Celgene	252-pt phase III (failed)	NCT01178281
Jakafi + LDE225	Novartis	82-pt phase I/II	NCT01787552
Jakafi + panobinostat	Novartis	61-pt phase I	NCT01433445
Simtuzumab	Gilead	54-pt phase II	NCT01369498
Jakafi + azacitidine	Incyte	Investigator-led, 50 pts	NCT01787487
Imetelstat	Geron	Investigator-led, 33 pts	NCT01731951
Givinostat	Italfarmaco	30-pt phase II	NCT01761968

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