Evaluate Vantage

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# ASH preview – Midostaurin sees the finish line at last

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Novartis's development of the FLT3 inhibitor midostaurin could at long last be nearing the finish line, courtesy of a large, investigator-sponsored acute myeloid leukaemia study whose results have been given pride of place at the ASH meeting's plenary session.

But the bigger question is whether this mechanistic approach is already getting stale, as suggested by the Swiss group's low-key presence in trials. Investors looking at ASH data outside the hot field of cell therapy will probably find more of interest in studies of venetoclax, a vital newcomer in chronic lymphocytic leukaemia, and the search for immunotherapy biomarkers (see table below).

Still, the organisers of ASH are clearly impressed by the midostaurin data, from the 712-patient CALGB 10603/Ratify study; midostaurin is the only novel agent to feature among the six ASH abstracts selected for the plenary session, which takes place on December 6.

The Ratify investigators had screened over 3,000 AML patients to identify those with the FLT3 mutation, and found that in these patients midostaurin reduced risk of death by 23% versus placebo (primary endpoint; p=0.007). Novartis plans to file midostaurin this year, but was only a collaborator in Ratify, which was sponsored by the Alliance for Clinical Trials in Oncology.

Midostaurin has been in trials for over a decade, and sellside consensus is for 2020 sales of only $124m, according to *EvaluatePharma*. Last year, Daiichi Sankyo bought Ambit, developer of the competing agent quizartinib, which remains in phase III (*Therapy focus – Leukaemia opportunity gives FLT a chance to take flight, October 1, 2014*).

An open-label study of quizartinib versus salvage chemo was profiled at last year's ASH meeting, with the researchers highlighting the then ongoing Ratify trial. Other agents with FLT3 kinase activity include CTI's pacritinib and Arog's crenolanib.

| Selected ASH presentations – small molecules and MAbs | | | |
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| **Project** | **Company** | **Abstract** | **Detail** |
| Midostaurin | Novartis | 6 | HR for overall survival of 0.77 vs placebo (p=0.007) in 717 patients with FLT3-mutated AML. |
| Quizartinib | Daiichi Sankyo | 2557 | FLT3-mutated AML, re-analysis of phII data in patients who failed salvage therapy or bone marrow transplant. |
| Pacritinib | CTI Biopharma | 58 | Subgroup analysis of phIII Persist-1 trial. |
| Crenolanib | Arog Pharmaceuticals | 3695 | Pharmacokinetics in relapsed/refractory FLT3-positive AML. |
| Venetoclax | Roche/AbbVie | 496 | Safety run-in of CLL14 study of venetoclax + Gazyva/chlorambucil in first-line CLL. |
| SGN-CD33A | Seattle Genetics | 454 | Combo with hypomethylating agents; 65% CR or CRi in 23 AML patients unfit for high-dose chemo. |
| Imbruvica | J&J | 495 | Resonate-2 study in first-line CLL. |
| Ublituximab + TGR-1202 | TG Therapeutics | 1538 | PhI activity in r/r B-cell NHL and high-risk CLL. |
| Ixazomib Oral | Takeda | 727 | PhIII Tourmaline study, HR for PFS of 0.742 vs Revlimid + dexamethasone alone (p=0.012). |
| Revlimid | Celgene | 25 | SWOG S0777 study in first-line MM, addition on top of Velcade + dexamethasone. |
| AG-221 | Agios | 323 | 74 responses in 181 patients with myeloid malignancies. |
| Opdivo | Bristol-Myers Squibb | 583 | PhI, 15 responses in 20 patients with r/r Hodgkin's lymphoma. |
| Keytruda | Merck & Co | 834 | Efficacy data from phII study in r/r CLL including Richter transformation. |
| Ponatinib | Ariad | 480 | Alternative to bone marrow transplant in CML with T315I mutation. |
| ABL001 | Novartis | 623 | Promising single-agent activity in CML patients who have failed prior TKI therapy. |

When the ASH meeting kicks off on December 4 cell therapy sessions are certain to generate some of the biggest attendances (*ASH preview – Cellectis steals the limelight, November 6, 2015*). But there is plenty to attract investors keen on more traditional approaches too, and these will likely eclipse midostaurin and its low forecasts.

A case in point is Roche/AbbVie's venetoclax, the most exciting new CLL treatment since Imbruvica, which its developers last week confirmed had been filed in the US in relapsed/refractory patients with the 17p deletion – a high-risk group. Roche has five separate oral sessions on venetoclax scheduled for December 7.

Investors will be scrutinising data for magnitude and duration of efficacy, as well as for tumour lysis syndrome – the serious side effect that had marred some earlier trials. Venetoclax threatens not only the CLL landscape, but also Seattle Genetics' strategy to evolve beyond Adcetris, which of course features in numerous abstracts.

Of particular interest could be the promising responses reported in a phase I trial of Seattle's novel AML conjugate SGN-CD33A. Leerink analysts say this efficacy is good, pending the full presentation of the tolerability profile, but reckon venetoclax looks better in this setting.

**Immunotherapy**

Elsewhere, while PD-1 and PD-L1 MAbs have taken huge strides in solid tumour indications like melanoma and lung cancer, their efficacy in haematological malignancies has underwhelmed (*ASH – A way in for anti-PD-1 therapy in haematology, December 6, 2014*).

Roche last week stressed the importance of atezolizumab as one of four doublets in trials for NHL, though this

will not feature at ASH. Opdivo and Keytruda are being profiled in ASH presentations, however, including in data from the latter's Keynote-023 study in multiple myeloma.

Investigators are particularly keen to identify new biomarkers or predictors of response. Judging by the early data, finding specific patient subgroups will be vital if PD-1/PD-L1 agents are to make inroads into haematology.

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