Evaluate Vantage

October 19, 2016

Collaborative leukaemia trial orbits moonshot initiative

Jonathan Gardner

The once-neglected blood cancer acute myeloid leukaemia has seen a flurry of activity of late – which might explain why four companies with mid-stage projects are taking the unusual step of getting involved in a collaborative study.

The Beat AML trial, led by the US Leukemia & Lymphoma Society, will evaluate Celgene's enasidenib, Boehringer Ingelheim's BI 836858, Gilead's entospletinib and Alexion's samalizumab as first-line therapies in patients aged over 60. AML studies commonly enrol relapsed or refractory patients so, if successful, the new trial could give the assets involved an edge over projects that are closer to the market (see tables below).

The over-60s are a population unable to tolerate intensive chemotherapy, the current first-line standard of care. The study will also analyse patients' genomic data before deciding what treatment they will receive.

This is important for Agios/Celgene's IDH2 inhibitor enasidenib, for one – it is being trialled in patients with IDH2 mutations, which are present in 10-15% of the adult AML population.

Enasidenib, previously known as AG-221, looks the closest to the market of the four projects in Beat AML. Celgene has said it plans to submit it to the FDA by the end of the year on the back of data from a phase I/II trial in relapsed/refractory disease (*Just like buses, three come at once in leukaemia regulatory queue, September 08, 2016*).

Enasidenib is already in a phase III trial in relapsed or refractory AML. Beat AML could add first-line disease to its repertoire.

New agents nearing

But the IDH2 inhibitor might be beaten to approval by Jazz Pharmaceuticals' Vyxeos, a liposomal preparation of cytarabine and daunorubicin, and Novartis's FMS-like tyrosine kinase 3 inhibitor midostaurin. The latter is targeting newly diagnosed patients, but is limited to the genetic subtype of FLT3-mutated AML.

Jazz is seeking approval for Vyxeos, which it gained through the acquisition of Celator, in older patients with secondary AML. The group started a rolling NDA in October.

These frontrunners look unlikely to be troubled by Boehringer's volasertib, which stumbled in its pivotal trial in June. The company said work would continue, but it is notable that it is also participating in the Beat AML with BI 836858, which being an anti-CD33 MAb has a different mechanism of action.

A dark horse in the AML race could be Cyclacel's sapacitabine, which is due to report data from the phase III Seamless study, in elderly patients with newly diagnosed AML, soon. However, expectations are low after the trial failed its interim futility analysis in December 2014 (*Event – Cyclacel's date with decitabine, August 22, 2016*).

In any case, the fact that genetic screening is being carried out in Beat AML could give the products involved a well-defined subgroup to target.

In this, the leukaemia trial is taking a page from the NCI-Match study in lung cancer, although the investigators will clearly need to be more cautious about obtaining higher-quality biopsies (*Vantage point – NCI initiative could see drugs for mutations, not tumour types, June 11, 2015*).

An additional model is provided in a second collaborative trial – Lung MAP, which has added new agents as research has progressed. The Leukemia & Lymphoma Society says other pharma companies have expressed an interest in joining Beat AML, and it could add more treatment arms, with a total of up to 10 mooted.

Competitive edge

Alexion looks like it is making a last throw of the dice with samalizumab, which reported phase I/II results in

2010, but it was last listed in the group's pipeline in 2011. Unlike the already submitted AG-221, this project is fortunate to have little competition in the CD-200 targeting class, where only Bristol-Myers has an early-stage asset.

Beat-AML projects and their competitors			
Pharmacology class	**Project**	**Company**	**Status**
Anti-CD200 MAb	ALXN6000 (samalizumab)*	Alexion/Dyax	Phase II**
	TTI-200.7	Bristol-Myers Squibb/Trillium Therapeutics	Preclinical
Anti-CD33 MAb	BI 836858*	Boehringer Ingelheim	Phase II
Anti-CD33 MAb-PBD conjugate	vadastuximab talirine	Seattle Genetics	Phase III
Anti-CD33/CD3 bispecific BiTE MAb	AMG 330	Amgen	Phase I
Anti-CD33 CAR-T cell therapy	Acute Myeloid Leukemia Research Project	Ziopharm Oncology/Intrexon/MD Anderson	Preclinical
Bispecific CD33/CD3 TandAbs antibody	AMV-564	Affimed/Amphivena Therapeutics	Preclinical
IDH-2 inhibitor	AG-221/CC-90007 (enasidenib)*	Celgene/Agios Pharmaceuticals	Phase III
IDH-1 inhibitor	AG-120	Agios Pharmaceuticals	Phase II
	BAY1436032	Bayer	Phase I
	IDH1 Mutant Selective Inhibitor Program	Daiichi Sankyo	Preclinical
	IDH305	Novartis	Phase I
IDH-1 & 2 inhibitor	AG-881	Celgene/Agios Pharmaceuticals	Phase I
Syk inhibitor	entospletinib*	Gilead Sciences	Phase II
	AB8779	AB Science	Preclinical
**Beat AML projects.*			
***Alexion has not listed ALXN6000 as an active project since 2011 and it had been assumed abandoned.*			

Likewise, Gilead's only blood cancer competitor looks like AB Science – the Syk inhibition class is largely being used for autoimmune, inflammatory and respiratory diseases. AB Science's AB8779 has undergone preclinical study in non-Hodgkin lymphoma and chronic lymphocytic leukaemia.

Boehringer's CD33-targeting antibody, on the other hand, has healthy competition in all the hot areas of oncology research, including adoptive T-cell therapies, antibody-drug conjugates and bispecific antibodies.

Any projects graduating from Beat AML should of course emerge with a built-in competitive advantage in a biomarker-defined subgroup, and will have generated these data in a trial that someone else helped pay for. It is not hard to see why companies would want to participate, although past studies of this type show that screening will need to be high quality for the effort to be judged a success.

To contact the writers of this story email Madeleine Armstrong or Jonathan Gardner in London at news@epvantage.com or follow @ByMadeleineA or @ByJonGardner on Twitter

Evaluate Americas
+1-617-573-9450

Evaluate APAC
+81-(0)80-1164-4754