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Therapy focus – Leukaemia opportunity gives FLT a chance to take flight

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Daiichi Sankyo's $315m takeout of Ambit Biosciences for the blood cancer project quizartinib shows how competition is heating up among agents active in the FLT3 kinase pathway. In spite of a fellow Japanese group, Astellas, dropping the agent last year, Daiichi clearly saw promise.

In acquiring the California-based biotech, Daiichi has picked up one of the more selective candidates acting on FLT3, dysfunction of which may result in more than three in 10 cases of acute myeloid leukaemia (AML). A healthy group of rivals, including Astellas's own entry, will be closely watching interim readout of quizartinib's phase III trial next year (see table).

Several products already on the market, including Bayer/Amgen's Nexavar and Pfizer's Sutent, already act on FLT3 (FMS-like tyrosine kinase 3), yet are used to treat solid tumours. What is changing in the space is that mutations in the FLT3 gene are known to be an important factor in development of AML – more than 30% are estimated to be related to FLT3 – and more selective molecules are emerging.

The internal tandem duplication mutation is connected with 23% of AML cases, is more likely than others to arise without a previous myelodysplastic disorder, and cannot be cured with chemotherapy alone. The chemotherapy regimen for AML is rigorous, requiring a month in hospital, and many elderly patients opt for palliative care instead.

Those who do choose chemotherapy often undergo haematopoietic stem cell transplantation on their first remission, another demanding therapy that requires both chemotherapy and immunosuppression to achieve. Thus, a targeted agent with fewer side effects will be most welcome in this disease.

Nearing critical data

A scan of the FLT3 pipeline finds quizartinib neck and neck for title of most advanced, but this certainly has not been in the clinic the longest of the active projects in development. That honour goes to Novartis's midostaurin (PKC412), an indolocarbazole that went into its first phase I trial in 2004, according to clinicaltrials.gov.

That class of compounds is known to have potent kinase inhibition properties; midostaurin binds to other targets such as the platelet-derived growth factor receptor, and Ambit points to the less selective properties of this agent as a weakness, although midostaurin has also been shown to be active against AML patients with another type of FLT3 mutation, in the tyrosine kinase domain.

FLT3 inhibitors in active development for leukaemia				
	Project	**Pharmacology class**	**Company**	**Trial ID**
Phase III	PKC412 (midostaurin)	FLT3 inhibitor	Novartis	NCT00651261; NCT01830361; NCT01883362
	Quizartinib	FLT3 inhibitor	Ambit Biosciences	NCT02039726
Phase II	ASP2215 (gilteritinib fumarate)	FLT3 & Axl kinase inhibitor	Astellas Pharma	NCT02014558
	AKN-028	FLT3 & c-KIT inhibitor	Akinion Pharmaceuticals	NCT01573247
Phase I	E6201	FLT3 & MEK-1/MEKK-1 inhibitor	Boston Strategics	NCT00794781
Preclinical	NMS-P948	FLT3 & KIT inhibitor	Nerviano Medical Sciences	–
	Aurora+FLT3 kinase program	Aurora & FLT3 inhibitor	Sareum	–
	SEL24-B489	PIM-1 kinase & FLT3 inhibitor	Selvita	–
Source: EvaluatePharma				

Midostaurin's most advanced trial is investigator-sponsored, being run by the Alliance for Clinical Trials in Oncology since 2008. It combines midostaurin with chemotherapy and could read out overall survival data in the middle of 2015. Certainly, analysts from Morgan Stanley expect this to be the case, and have pencilled in sales of $500m in 2020; the *EvaluatePharma* consensus is $90m, a number that would rise on positive data.

Hot on midostaurin's heels is quizartinib. This targeted kinase inhibitor is the only one in active development that has limited action outside FLT3.

Ambit promoted this as an important differentiating factor, although this was not sufficient to keep Astellas on board as a development partner – the Japanese group dropped out of the deal after readout of the phase II Ace trial. Astellas has since revealed that it is working on its own candidate in this space.

Quizartinib's phase III Quantum-R trial is against salvage chemotherapy in 326 patients resistant to treatment or relapsed within six months of finishing first-line therapy. An interim readout is expected in the second half of 2015, which could lead to filing; the primary endpoint is overall survival.

Sacrificing quizartinib

Astellas's entry, ASP2215, is an inhibitor of both FLT3 and the AXL kinase, and the group recently revealed that it would accelerate its development.

With other projects ahead of it or drawing even in phase II, this is no surprise. ASP2215's most advanced study is dose escalation in relapsed/refractory AML patients – results are likely to come out sometime next year – although Astellas has tantalisingly filed a phase I trial in newly diagnosed patients.

The other phase II asset is owned by Sweden's Akinion Pharmaceuticals, a Swedish Orphan Biovitrum spin-out jointly owned with Karolinska Development to nurture AKN-028. This combined FLT3 and c-KIT inhibitor began a European dose-escalation trial in 2012, with an expected conclusion date in 2014. The group has disclosed little about the trial, however.

Phase I is occupied by E6201, which also acts on the MEK-1 pathway. That former Eisai project is now in the hands of Boston Strategics, which licensed global rights in June; a proof-of-concept trial in cancer is planned, although its new owner has not disclosed when. Eisai has gone as far as phase II in severe psoriasis, and its phase I dosing trial in oncology has been in patients with solid tumours.

Italian-based Nerviano Medical Sciences published preclinical data on its FLT3 candidate in 2012, but has not prominently featured it. Meanwhile, Selvita has announced plans to move SEL24-B489, an FLT3 and PIM-1 kinase inhibitor, into the clinic in 2015. The Polish group published preclinical data at the AACR meeting in April. The UK's Sareum, meanwhile, has nominated a lead candiate from its Aurora + FLT3 programme and signed a development deal in China.

Next year should prove to momentous for development in the FLT3 pathway; Novartis will find out whether its prolonged investment in midostaurin was sensible, while Daiichi will learn whether its $315m gamble will pay off. Those that have followed will await the news keenly.

This article has been updated to reflect Sareum's preclinical Aurora + FLT3 kinase project.

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