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Therapeutic focus – New agents nip at Jakafi's heels in myelofibrosis

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Treatment of myelofibrosis experienced a advance in 2011 when the Jak-1/2 inhibitor Jakafi was introduced as the first drug indicated specifically for the haematological condition. Now several similar compounds are crowding the late-stage pipeline hoping to succeed in blocking the faulty Janus kinases that trigger the characteristic dysfunctional blood cell production in the bone marrow.

As Jakafi was effective in relieving patients' enlarged spleens but unable to relieve anaemia, there is opportunity to challenge, and Jaks from Sanofi, Cell Therapeutics and Gilead Sciences will be hoping to do just that. Also waiting in the wings are drug classes aimed at other biological targets, such as histone deacetylase (HDAC) and a variety of signalling pathways (see table).

Something new

An illustration of the variety of approaches is provided by the nearing readout of data for Geron's telomerase inhibitor imetelstat, which has failed in multiple types of cancer but is hoped will have an effect in myeloproliferative disorders (*Geron bets its stake in haematological disease, September 24, 2013*). As telomerase inhibition reduces the effect of an enzyme that prevents cell death, researchers believe imetelstat could control disease by attacking malignant progenitor cells.

It seems reasonable to try telomerase inhibition. In myelofibrosis, mutated hematopoietic stem cells cause the production of abnormal blood cells in the marrow, shifting the production of normal blood cells into other organs, such as the spleen. Anaemia, fatigue and spleen swelling are some of the main symptoms.

Another characteristic of myelofibrosis is overproduction of platelets, triggering an immune response from cytokines in the marrow, which leads to fibrosis. The fibrosis also impedes blood cell production.

More than 12,000 people are estimated to have myelofibrosis in the US. Median survival exceeds 10 years for asymptomatic patients younger than 65 without anaemia or elevated white-blood cell or blood blast cell counts. Those with two or more symptoms can expect to live less than three years.

Jaks are better?

Though unique in the space in terms of its mechanism of action, Geron's agent is leaping into a packed field of candidates looking to take on Incyte's Jakafi, which is marketed outside the US as Jakavi by Novartis. This year, its first full year on global markets, the drug is forecast to sell $373m, rising to $1.39bn in 2018, according to *EvaluatePharma*'s consensus. Expansion into polycythaemia vera is expected in the next couple of years, which is predicted to boost sales.

Before Jakafi, treatments included chemotherapy to kill rapidly dividing malignant cells; immunomodulators like Revlimid, androgen therapy like oxymetholone, or corticosteroids like prednisone to boost blood-cell counts; and bisphosphonates to relieve bone pain. Regulators approved Jakafi on the basis of significant improvements in spleen size and total symptom score, which took in abdominal discomfort, pain, night sweats, itching and early satiety.

Jakafi did not, however, have a positive impact on anaemia – in fact the condition was exacerbated by its use. Given that haemoglobin levels below 10 grams per decilitre are an independent prognostic factor in addition to the symptoms that Jakafi relieves – and may be the most important factor affecting survival – there is room for improvement on Incyte's entry.

Furthermore, it is not clear whether Jakafi's effect on the spleen is a result of Jak 1 blockade, which regulates inflammatory response, or Jak 2, which modulates blood-cell production.

Myelofibrosis pipeline								
				WW sales (indication) ($m)				
Status	**Product**	**Company**	**Pharmacological Class**	**2012**	**2013**	**2014**	**2016**	**2018**
Marketed	Jakafi/Jakavi	Incyte/Novartis	Jak-1/2 inhibitor	153	360	526	714	744
Phase III	SAR302503	Sanofi	Jak-2 inhibitor	-	-	14	131	259
	Pacritinib	Cell Therapeutics/S*Bio	Jak-2 inhibitor	-	-	-	50	125
Phase II	CYT387	Gilead Sciences	Jak-1/2 inhibitor	-	-	-	11	119
	BMS-911543	Bristol-Myers Squibb	Jak-2 inhibitor	-	-	-	4	15
	Imetelstat	Geron	Telomerase inhibitor	-	-	-	-	-
	CEP-701/KT5555	Teva Pharmaceutical Industries/Kyowa Hakko Kirin	Trk tyrosine kinase inhibitor	-	-	-	-	-
	LY2784544	Eli Lilly	Jak-2 inhibitor	-	-	-	-	-
	Simtuzumab	Gilead Sciences	Anti-lysyl oxidase-like-2 (LOXL2) MAb	-	-	-	-	-
	PEGIntron	Merck & Co	Interferon alpha	-	-	-	-	-
	LBH589	Novartis	Histone deacetylase (HDAC) inhibitor	-	-	-	-	-
	INCB39110	Incyte	Jak-1 inhibitor	-	-	-	-	-
	NS-018	Nippon Shinyaku	Jak-2 inhibitor	-	-	-	-	-
	Pracinostat	MEI Pharma/S*BIO	Histone deacetylase (HDAC) inhibitor	-	-	-	-	-
	LDE225 & Jakafi	Novartis	Hedgehog pathway/smoothened (SMO) inhibitor & Jak-1/2 inhibitor	-	-	-	-	-
Phase I	BKM120	Novartis	Phosphatidylinositol 3-kinase (PI3K) inhibitor	-	-	-	-	-

Looking for an edge

The next Jak waiting in the wings is Sanofi's fedratinib (SAR302503), which reported positive data from its Jakarta study in May (*Event – Sanofi hopes its JAK will not be a dull boy, May 13, 2013*). The French group has disclosed little beyond meeting the primary endpoint, the proportion of patients achieving at least 35% reduction in spleen volume. Full data are being held for a medical meeting, with the Ash congress in December being a logical forum.

Cell Therapeutics and S*Bio's pacritinib is also in phase III. Onyx Pharmaceuticals had signed an option but did not exercise it, and Cell Therapeutics picked up the agent in 2012. Trial data should be available in the latter half of 2014 – again, spleen shrinkage and overall symptomatic scores are the chief endpoints.

Trying to differentiate itself from the these Jak inhibitors is Gilead Sciences' CYT387, for which it bought Canadian group YM Biosciences last year (*Gilead hopes acquisition JAKs up oncology pipeline, December 12, 2012*). That takeout also brought on board simtuzumab, an antibody that blocks the lysyl oxidase-like-2, an enzyme that regulates fibrogenesis, which is in phase II in myelofibrosis.

The CYT387 phase I/II programme was able to show it could reduce transfusion dependency. With Jaks from

Bristol-Myers Squibb, Eli Lilly and a new one from Incyte, differentiation will be an important factor in achieving market share.

When it was approved, Jakafi represented a step forward for myelofibrosis patients. However, given that elimination of anaemia and other disease markers can help to improve patient survival, Jakafi clearly can be improved upon.

All data sourced to EvaluatePharma

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