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EHA – Daiichi data set quizartinib up for regulatory review

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Acute myeloid leukaemia has for years been one of the most underserved diseases in oncology, with chemotherapy almost a given as frontline treatment until last year. But things are changing with two targeted agents, Novartis's Rydapt and Celgene's Idhifa, having arrived recently. Now Daiichi Sankyo's quizartinib is making a good case that it should join the AML chase.

Data from the Quantum-R trial showed that quizartinib monotherapy significantly reduced the risk of death by 24% compared with salvage chemotherapy in patients with FLT3 mutations who have relapsed on first-line regimens. Daiichi wisely chose the relapsed/refractory setting to avoid going immediately against Rydapt, itself claimed to be an inhibitor of FLT3, among other targets, but an equally important finding is that the data support treatment with quizartinib after progression on Rydapt.

Daiichi says it plans to submit quizartinib to regulators for approval based on the Quantum-R data. The Japanese company has a study under way called Quantum-First comparing first-line quizartinib plus chemo versus chemo alone – the same setting in which Rydapt won approval. That study is due to read out by 2020.

Single kinase

While Rydapt is indicated in the first-line setting for patients with FLT3 mutations it is not, as originally believed, a specific FLT3 inhibitor – it also binds with the platelet-derived growth factor receptors CDK1 and VEGFR.

Quantum-R's enrolment criteria specifically excluded prior FLT3-directed therapy – except for Rydapt, which the Clinicaltrials.gov entry calls a "multi-kinase inhibitor". The rationale is presumably that even if Rydapt does hit FLT3 its affinity for this kinase is insufficient.

Thus, the logic goes, there is a rationale for a second-line FLT3-specific treatment like quizartinib. Of course, if this is true it makes Rydapt's use in FLT3-mutated AML seem questionable.

In Quantum-R patients taking quizartinib had an overall survival of 6.2 months, against 4.7 months for patients on salvage chemotherapy, defined as one of three regimens with cytarabine as a backbone. Patients on quizartinib had a 69% overall response rate and 12.1-week duration of response, versus 30% and five weeks for chemo; 32% of the quizartinib subjects went on to have a stem cell transplant, against 12% of the chemo recipients.

Daiichi is known more for its cardiovascular and central nervous system drugs, and has like so much of the sector redirected a substantial amount of cash to oncology. Its three biggest pipeline projects are the antibody-drug conjugate DS-8201 for breast cancer, pexidartinib in tenosynovial giant cell tumor, and quizartinib; the last two came from acquisitions of Plexxikon and Ambit Biosciences respectively.

AML chase

In AML Daiichi is entering an increasingly crowded space, as eight new agents are forecast to be launched in the next three years. Besides Rydapt, Astellas's gilteritinib also targets FLT3 mutations – however, both of those are active on other kinases and Daiichi will obviously hope that a more precise kinase inhibitor like quizartinib will be more effective.

Acute myeloid leukaemia outlook					
		Global sales ($m)			
Project	**Company**	**2018e**	**2020e**	**2022e**	**2024e**
Ivosidenib	Agios Pharmaceuticals	37	386	633	844
Venclexta	Abbvie	-	165	415	657
Gilteritinib	Astellas Pharma	1	192	447	652
SL-401	Stemline Therapeutics	16	226	439	629
Amnolake	Syros Pharmaceuticals	-	115	260	595
Rydapt	Novartis	193	390	518	559
Idhifa	Celgene	83	237	370	498
ARGX-110	Argenx	-	-	100	411
Quizartinib	Daiichi Sankyo	0	106	195	284
UCART123	Cellectis	-	63	163	282
Source: EvaluatePharma.					

IDH inhibition is the mechanism used by Celgene's Idhifa and Agios's ivosidenib (AG-120), while Abbvie's Venclexta is a Bcl2 inhibitor, Stemline's SL-401 is a conjugate containing IL-3, Syros's Amnolake is retinoic acid receptor alpha agonist, and Argenex's ARGX-110 is an anti-CD70 MAb. And no haematological cancer pipeline would be complete without a CAR-T entry, that being Cellectis's UCART123.

Quizartinib is not forecast to reach the blockbuster numbers that Daiichi's big oncology asset, DS-8201, is expected to hit, but it does need to meet expectations if the company's shift into oncology is to be judged a success. Getting approval in second-line AML will be a good start, but quizartinib probably needs to take on Rydapt head to head to really fulfil its promise.

Trial	ID
Quantum-R	NCT02039726
Quantum-First	NCT02668653

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