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The world's twelfth VEGF drug will be sold by Takeda

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The Japanese company keeps the licensing fires burning with a $400m deal for Hutchmed’s fruquintinib.

Hutchmed has followed through on a recent promise to focus on its most advanced assets by licensing western fruquintinib rights to Takeda. The deal terms might surprise some: Takeda has handed across $400m up front, a seemingly large amount for what could ultimately become the 12th drug acting on VEGF to come to the US market.

Perhaps this is slightly unfair; as a next-generation tyrosine kinase inhibitor fruquintinib offers greater specificity against VEGFR than most other drugs, and its primary indication, colorectal cancer, is relatively uncrowded for this mechanism. Either way, investing in US launch would have gone against Hutchmed’s pledge, so Takeda’s generosity has provided a big boost.

It was last November that Hutchmed, citing tough market conditions, announced a move to prioritise late-stage approvals to speed its path to profitability. Early-stage assets would be deprioritised, it said, and partners for markets outside China would be sought.

Fruquintinib is already marketed in China, having been approved in 2018 as Elunate for third-line colorectal cancer on the basis of the Fresco study. It is licensed locally to Lilly, which had an option on US rights, but which turned down this option, likely because it already sold a VEGF-acting drug for colorectal cancer, namely Cyramza.

2023 filing

The basis for getting fruquintinib approved in the US is the Fresco-2 study, whose results were presented at last year’s Esmo meeting, and which is expected to lead to US and Europe filings this year.

In Fresco-2, which enrolled colorectal cancer patients who had failed at least two lines of therapy, fruquintinib yielded median overall survival of 7.4 months, versus 4.8 months for standard of care, cutting risk of death by 34% ($p<0.001$). Severe adverse events were seen in 63% of patients, versus 50% for control, and the most common were hypertension, asthenia and hand-foot syndrome.

In addition to the $400m up front for ex-China rights, Takeda has pledged up to $730m in milestones, plus royalties on sales. In 2028 *Evaluate Pharma* sellside consensus sees Elunate selling $264m in China and $303m elsewhere; for Takeda to get a decent return on its investment it will likely want to pursue broader uses

than the late-line colorectal indication.

But can it achieve this? Fruquintinib is one of many small-molecule drugs acting on VEGFR, and the competition includes the antibodies Cyramza and Avastin, though the latter, from Roche, hits soluble VEGF rather than its receptor.

However, the chief uses for these drugs are renal and liver cancers, and only Cyramza and Bayer's Stivarga carry colorectal cancer on their approved labels. Fruquintinib can be said to be differentiated from the former because it is a small molecule, and from the latter because it is much more specific for VEGFR1, 2 and 3.

Lacking specificity

It is probably this last attribute that works most in Takeda's favour. The anti-VEGFR space is typified by lack of specificity, and only Pfizer's Inlyta appears to be a relatively precise inhibitor of VEGFR1, 2 and 3; Inlyta reached phase 2 in colorectal cancer, but the use is no longer being pursued.

The rest of these drugs have broad tyrosine kinase activity, a fact that likely contributes to poor safety profiles. Stivarga is probably an extreme example of a so-called "dirty" multi-kinase drug, inhibiting Ret, c-Kit, PDGFRα and β, FGFR1 and 2, Tie-2, DDR2, TrkA, EphA, Raf-1, Braf, SAPK2, PTK5, Abl and CSF1R in addition to VEGFR1, 2 & 3.

If fruquintinib is seen to be a relatively clean, next-generation drug it could be pushing at an open door in colorectal cancer, but Takeda will surely push harder still.

Selected drugs acting on VEGF			
Drug	**Company**	**Mechanism**	**US approved cancer uses**
Avastin	Roche	MAb vs VEGF	Renal, colorectal, brain, cervical, ovarian & liver
Cyramza	Lilly	MAb vs VEGFR2	Colorectal, liver, NSCLC & gastric/GEJ
Sutent	Pfizer	TKI vs VEGFR1, 2 & 3, PDGFR & others	Renal, GIST & pNET
Nexavar	Bayer	TKI vs VEGFR1, 2 & 3, PDGFR & others	Renal, liver & thyroid
Fotivda	Aveo	TKI vs VEGFR1, 2 & 3, PDGFR & others	Renal
Cabometyx/ Cometriq	Exelixis	TKI vs VEGFR1, 2 & 3 & others	Renal, liver & thyroid
Votrient	Novartis	TKI vs VEGFR1, 2 & 3, FGFR, PDGFR & others	Renal
Stivarga	Bayer	TKI vs VEGFR1, 2 & 3, FGFR, PDGFR & others	Colorectal
Lenvima	Eisai	TKI vs VEGFR1, 2 & 3, FGFR, PDGFR & others	Renal, liver & thyroid
Caprelsa	Sanofi, ex Astrazeneca	TKI vs VEGFR1, 2 & 3, EGFR & others	Thyroid
Inlyta	Pfizer	TKI vs VEGFR1, 2 & 3	Renal
Elunate	Hutchmed/ Lilly/ Takeda	TKI vs VEGFR1, 2 & 3	None (China approved for colorectal)

TKI=tyrosine kinase inhibitor. Source: prescribing information & scientific publications.

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