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Go or no go? Enhertu’s destiny revealed and FDA decisions due for Epizyme, Novo

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Enhertu gets an early thumbs up from the FDA – now decisions are due for Epizyme’s tazemetostat and Novo Nordisk's Rybelsus and Ozempic.

Christmas came early for Astrazeneca and Daiichi on Friday with the surprise approval of the companies’ breast cancer drug Enhertu. The antibody drug conjugate, which had been due a decision in April, joins an impressive list of quick decisions by the US regulators, including Seattle’s Padcev, an antibody-drug conjugate for bladder cancer, and Vertex’s Trikafta. November alone saw five drugs get approved early.

Enhertu, known generically as trastuzumab deruxtecan, was granted accelerated approval after showing a 60.9% response rate in the phase II Destiny-Breast 01 trial, striking efficacy for such heavily pretreated breast cancer patients. The drug does, however, come with a black box warning of interstitial lung disease; the label cites a rate of 9% with fatalities of 2.6% out of a pooled safety database of 243 patients.

The question now is whether this toxicity signal will hold back use in earlier-stage patients; ambitious sales forecasts currently sit at $2.5bn in 2024, according to *EvaluatePharma*. Some analysts have said peak sales could reach $7bn. This will depend on the drug's performance in earlier settings where phase III trials are currently underway, including Destiny-Breast 02 against Herceptin and chemotherapy in those who have progressed on Roche's Kadcyla.

Ringing in 2020

Looking to next year Epizyme’s troubled epitheliod sarcoma drug tazemetostat will likely get approved after gaining a universal endorsement by an advisory panel in December. The drug had been plagued by safety concerns that led to a previous clinical hold, but the panel seemed to put these to bed with Leerink analysts noting that the potential risk of secondary malignancies appeared to be of minimal concern to both panellists and the FDA.

Despite limited phase II data showing relatively modest response rates in epitheliod sarcoma the panel considered the proportion and duration of responses to be clinically meaningful. The serious lack of approved therapies will also play in tazemetostat's favour, though a confirmatory trial is expected. Epizyme recently filed the drug in relapsed or refractory follicular lymphoma, a larger opportunity.

Another positive advisory committee came for Aimmune’s Palfozia in September, although investor opinion was mixed and questions remain about the long-term benefits, particularly versus peanut avoidance. Prospects

for Palfozia are hard to call and a critical report by the cost watchdog Icer has concluded that the project will likely be too expensive, which could have ramifications for the drug's commercial potential.

Rimegepant ODT, Biohaven's fast-acting oral dissolving tablet formulation, also known as Zydis ODT, is due a decision in acute migraine and will come hot on the heels of Allergan's offering ubrogepant, which is due a regulatory decision any day now. Zydis ODT is said to start working in 45-90 minutes.

The traditional pill formulation, known just as rimegepant, is also filed with a decision due by the middle of 2020.

Analysts have placed their bets on Biohaven's projects, with sales forecast to reach $897m for the rimegepant franchise, versus ubrogepant's $302m.

Notable first-time US approval decisions due in January			
Project	**Company**	**PDUFA date**	**Product NPV ($m)***
Travivo	Fabre-Kramer Pharmaceuticals	Jan 22 (estimate)	-
Tazemetostat	Epizyme	Jan 23	2,062
Dificid (oral suspension)	Merck/Astellas	Jan 24	490 (tablet and suspension)
AR101/Palfozia	Aimmune	Late January	1,889
Rimegepant ODT/Zydis ODT	Biohaven	Q1	1,733 (franchise)
**NPV data 20 December. Source: EvaluatePharma.*			

Supplemental approvals due

Novo has a double whammy early next year with decisions on the cardiovascular risk reduction indication for both Rybelsus and Ozempic, based on pooled data from the Pioneer 6 and Sustain 6 studies. The trials found a respective 21% and 26% reduction in major adverse cardiovascular events with these products versus placebo. But Pioneer 6 only showed non-inferiority, not superiority, while Sustain 6 did not include a prespecified superiority analysis – hence the pooling of the data.

It is therefore far from clear whether either drug will get the cardiovascular go-ahead, and Novo might have to wait for data from bigger cardiovascular outcomes trials such as the 9,600-patient Soul study of Rybelsus, which began earlier this year.

Imfinzi could move into first-line small cell lung cancer with its latest regulatory decision – however, it is unlikely to unseat Roche's Tecentriq as the go-to treatment. Imfinzi's Caspian trial showed a 13-month overall survival, combined with chemotherapy, comparable to Tecentriq, which was approved in this setting in March. Meanwhile another competitor is fast approaching with data due any day: Merck's Keytruda, with its Keynote-604 study. This is a real threat to Tecentriq's crown.

More on Keytruda, this time in high-risk non-muscle-invasive bladder cancer that is unresponsive to Bacillus Calmette Guerin therapy. A panel in December was largely positive but there were concerns over efficacy. The phase II Keynote-057 study showed a three-month complete response rate of 41% with a median duration of 16.2 months. At one year 46% of initial responders remained responsive, representing 19% of all patients included in the efficacy analysis – below the 30% bar recommended by the International Bladder Cancer group. Merck is currently running a confirmatory trial called Keynote-676. If given the green light in January Keytruda would be the first PD-(L)1 approved in this setting.

With the FDA's recent flurry of early approvals it is likely the list below could see some additions. For a more in depth look at what to expect next year check out Vantage's preview of 2020, free to download now.

Supplementary and other notable approval decisions due in January			
Product	**Company**	**Event type**	**Date**
Keytruda	Merck	sBLA for high risk non-muscle invasive bladder cancer, with carcinoma in situ that's unresponsive to standard Bacillus Calmette-Guérin therapy, based on Keynote-057	Jan
Ozempic and Rybelsus (oral semaglutide)	Novo Nordisk	sNDA for cardiovascular risk reduction, based on Sustain 6 and Pioneer 6	Jan
Dificid (tablet)	Merck/Astellas	sNDA for Clostridium difficile infections in children aged six months or older, based on Sushine	Jan 24
Imfinzi	Astrazeneca	sBLA for first-line small-cell lung cancer, based on Caspian	Q1
Source: EvaluatePharma, clinicaltrials.gov.			