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Despite Imfinzi, US accelerated approvals surge

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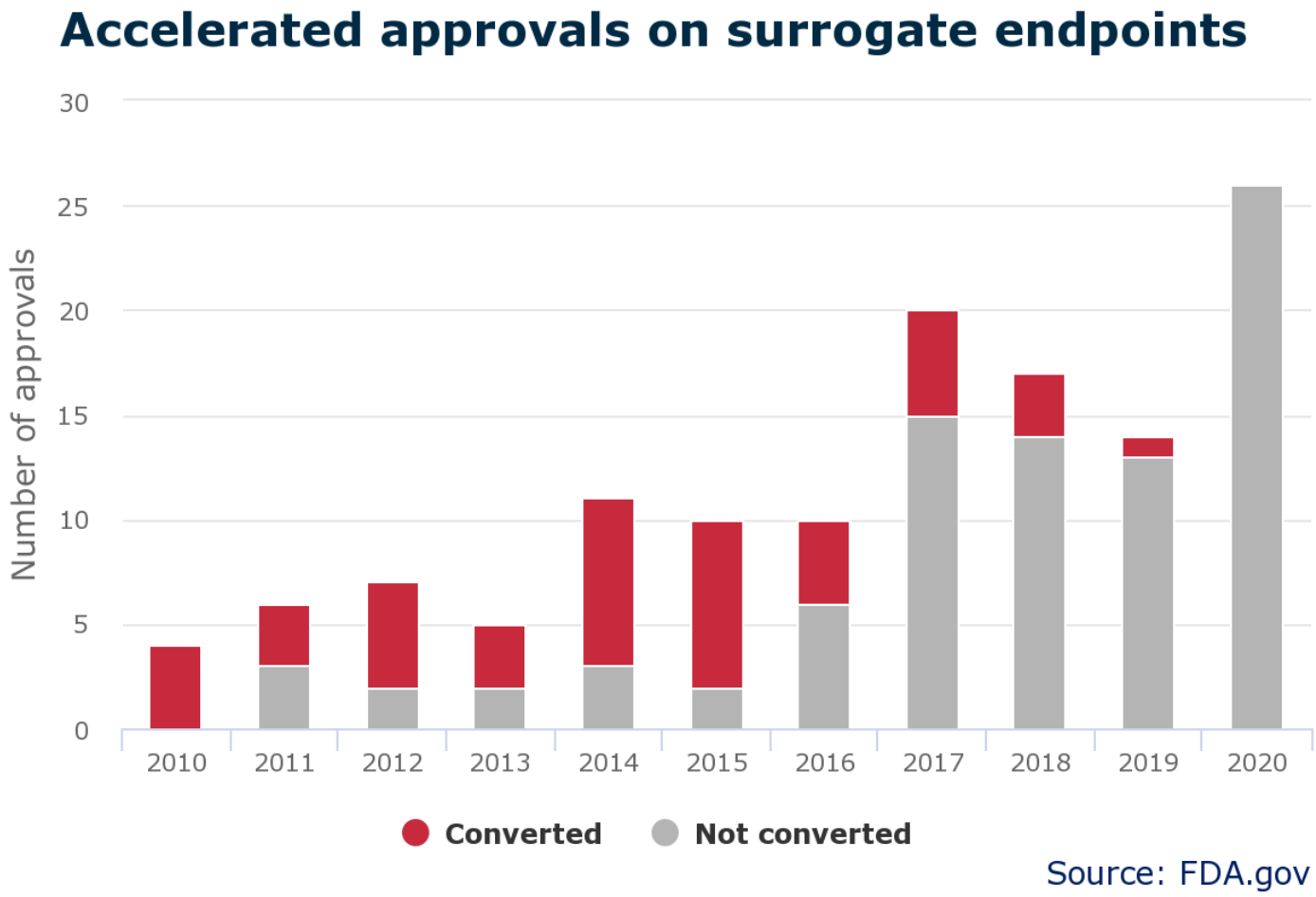
More and more drugs are being approved conditionally on flimsy data, and Imfinzi is just the second to be pulled after failing a confirmatory trial.

Today's US withdrawal of Astrazeneca's Imfinzi in urothelial bladder cancer was a long time coming. Imfinzi was among five anti-PD-(L)1 drugs approved for this cancer, going back nearly five years, and despite the failures of several subsequent studies the most the FDA had done was to seek to narrow the scope of some US labels.

This is the problem with accelerated approvals in immuno-oncology: they tend to be granted on flimsy surrogate endpoints subject to confirmation in a more robust setting, but when such confirmatory trials fail the agency seems to lack the teeth to get tough and rescind. And yet, accelerated US approvals are now occurring more frequently than ever before, an analysis by *Evaluate Vantage* suggests.

The latest cut of data supplied by the agency shows that 26 accelerated approvals were granted last year; the highest annual total previously was 20 in 2017. And only 44 of the 130 accelerated approvals granted in 2010-20 have been converted to formal green lights backed by confirmatory data.

Even more remarkably, a grand total of one such approval had been withdrawn during this time frame. That was Bristol Myers Squibb's Opdivo, pulled late last year in small-cell lung cancer, a 2018 accelerated approval that was followed just a year later by the failures of two confirmatory studies.



Perhaps we are now seeing something of a turning of the tide in terms of regulatory tolerance. Like Opdivo, Imfinzi has been withdrawn voluntarily after discussions with the FDA, but it is inconceivable that the agency did not apply at least some pressure on both companies to bring this about.

In Imfinzi's case initial urothelial bladder cancer approval was granted in 2017 – this was actually the drug's first ever US green light – on the basis of remission rates in Study 1108. Last year Imfinzi with or without tremelimumab failed to extend overall survival versus standard of care in the confirmatory Danube trial, and Astra cited this as the reason for today's withdrawal.

It has long been evident that urothelial bladder is one cancer type where checkpoint blockade was struggling to make an impact – the notable exception, of course, being Pfizer/Merck KGaA's Bavencio in the first-line maintenance setting of the Javelin Bladder-100 study. Merck & Co's Keytruda and Roche's Tecentriq have had their front-line labels narrowed, though both remain on the market.

Another tumour type to watch is liver cancer; here Opdivo and Keytruda have accelerated second-line approvals, and both have failed potentially confirmatory studies. Tecentriq is approved first line, a setting in which Keytruda was last year knocked by a US complete response letter.

Even if market withdrawals now become more common than before, the FDA looks unlikely to ease up on granting accelerated approvals any time soon.

Anti-PD-(L)1 drugs with accelerated US approvals and failed confirmatory trials			
Drug (company)	**Indication**	**Failed potentially confirmatory trial(s)**	**Regulatory outcome**
Keytruda (Merck & Co)	Urothelial bladder cancer (2L/1L)	Keynote-361 (1L)	US label narrowed
	Liver cancer (2L)	Keynote-240 (2L)	None
	Gastric/GEJ adenocarcinoma (3L)	Keynote-061 (2L) & 062 (1L, inconclusive)	None
	SCLC (3L)	Keynote-604 (1L)	None
Tecentriq (Roche)	Urothelial bladder cancer (1L)	Imvigor-211 (2L)	US label narrowed
	TNBC (1L)	Impassion-131 (1L)	None
Opdivo (BMS)	Liver cancer (2L)	Checkmate-459 (1L)	None
	SCLC (3L)	Checkmate-331 (2L) & 451 (1L)	Voluntarily withdrawn
Imfinzi (Astrazeneca)	Urothelial bladder cancer (2L)	Danube (1L, tremelimumab combo)	Voluntarily withdrawn
Source: company information.			