Evaluate Vantage

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Merck & Co makes the accelerated approval pathway its own

Jacob Plieth

Since 2010 14% of US accelerated approvals have been granted to Merck & Co's Keytruda.

In the last 11 years Merck & Co received 18 US approvals on an accelerated basis, more than any other company, updated numbers from the FDA show. An even more astonishing fact is that all of these relate to just one drug: Keytruda.

In this respect Merck is unique, but it is not the only company to have made extensive use of this special pathway, designed to allow drugs for truly unmet diseases to be green-lit with the backing only of surrogate endpoints. Roche and Bristol Myers Squibb also feature extensively, and oncology accounts for the vast majority of the 130 drugs approved this way.

82% of accelerated approvals since 2010 have concerned cancer drugs, with the 11 conditional green lights for Bristol's Opdivo coming just behind Keytruda's 18. Only three of Opdivo's accelerated approvals have been formalised by way of a confirmatory trial, with those yet to be converted including a 2016 nod for third-line classical Hodgkin lymphoma.

The issue of accelerated approvals that are still in place despite the failure of confirmatory trials is becoming prominent. Opdivo's SCLC indication was at last pulled last year for this reason, and yesterday Astrazeneca decided on a similar fate for Imfinzi in urothelial bladder cancer (*Despite Imfinzi, US accelerated approvals surge, February 22, 2021*).

Another major user of the accelerated approval process is Roche, which has used it for Alecensa, Perjeta, Polivy, Rozlytrek, Tecentriq (three green lights) and Gavreto (two); the first two have been confirmed.

In addition to Opdivo and Istodax, Bristol's accelerated approvals comprise Yervoy, Sprycel and Celgene's Pomalyst.

Withdrawals

The numbers come from the FDA's twice-yearly summary of accelerated green lights, and as at the end of last year Opdivo in SCLC was the only such drug to have been withdrawn.

This might come as a surprise. For instance, Lilly in 2019 said it was moving to withdraw Lartruvo, which had failed its confirmatory study; however, either because this has not formally happened or because a special

access programme is in place for existing patients, the drug remains on the approved list.

For several other drugs the long overdue lack of backing by a confirmatory trial is irrelevant, as they now record negligible sales. These include Aurobindo's Marqibo and Beleodaq, Bristol's Istodax and Novartis's Farydak.

The most conditionally approved cancer drugs			
		Accelerated US approvals	
Drug	**Company**	**Total granted**	**Converted to formal approval**
Keytruda	Merck & Co	18	6
Opdivo	Bristol Myers Squibb	11	3*
Imbruvica	Abbvie/J&J	4	1
Afinitor	Novartis	3	3
Tecentriq	Roche	3	0
Adcetris	Seagen	2	2
Venclexta	Roche/Abbvie	2	2
Bavencio	Merck KGaA/Pfizer	2	1
Blincyto	Amgen	2	1
Pomalyst	Bristol Myers Squibb	2	1
Rubraca	Clovis	2	1
Xpovio	Karyopharm	2	1
Gavreto	Roche/Blueprint	2	0
Tazverik	Epizyme	2	0
Vitrakvi	Bayer	2	0
Yervoy	Bristol Myers Squibb	2	0
*Note: *1 withdrawn. Source: US FDA data for 2010-20.*			

Only 23 accelerated approvals since 2010 concern non-cancer drugs, amounting to 17 individual products, only two of which, Novartis's Exjade and Boehringer Ingelheim's Praxibind, have converted to full approvals on the back of confirmatory trials.

Perhaps the most controversial among these is Sarepta's duo of Duchenne muscular dystrophy exon skippers, Exondys 51 and Vyondys 53, approved in 2016 and 2019 respectively. Exondys's confirmatory MIS51ON study only began last year – after scathing comments from the FDA – while the latter's, called Essence, will not read out until 2024.

Yet, based on flimsy surrogate endpoints, the two drugs look set to record combined sales in excess of $500m, according to *EvaluatePharma's* consensus of sellside estimates.

+1-617-573-9450

Evaluate APAC
+81-(0)80-1164-4754