Evaluate Vantage

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Go or no go? Oncology decisions ahead for the FDA

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The US regulator will provide verdicts on cancer projects from TG and Athenex, while Sarepta aims for its third Duchenne approval.

Cancer approval decisions look set to dominate the US regulator's time in February, but further delays due to the coronavirus pandemic cannot be ruled out. GSK's dostarlimab was the latest to fall victim to a manufacturing inspection delay, and a decision on the checkpoint inhibitor is now due in the first half of 2021.

One of the more important oncology approvals that had been expected in February − of the combination of Exelixis/Ipsen's Cabometyx and Bristol Myers Squibb's Opdivo in first-line renal cell carcinoma − came late last week. Opdivo is forecast to dominate the renal cell cancer space by 2026 with sales of $2.9bn, according to *EvaluatePharma* consensus.

Elsewhere, TG Therapeutics hopes to gain its first approval by February 15. The company's PI3K delta inhibitor umbralisib is due a decision for use in patients with marginal zone lymphoma who have received at least one prior anti-CD20-based regimen.

The filing was based on data from the Unity-NHL study of patients with marginal zone lymphoma, follicular lymphoma or small lymphocytic lymphoma. Umbralisib-treated marginal zone lymphoma patients showed an overall response rate of 49%, according to data presented at last year's Ash conference − meeting the group's target of 40-50%.

On safety, the most common grade 3 adverse events were neutropenia, diarrhoea and increased liver enzymes across the patient groups. Notably, other approved PI3K inhibitors like Zydelig and Copiktra have black box warnings of fatal diarrhoea, colitis and infections.

An FDA decision is also set for June for umbralisib in follicular lymphoma, while a bigger opportunity lies ahead with a combination with ublituximab, an anti-CD20 antibody. TG started a rolling submission at the end of last year for the combination's use in CLL.

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Athenex's lead cancer programme, Oraxol, a combination of oral paclitaxel and encequidar, has a Pdufa date towards the end of February for use in metastatic breast cancer. Encequidar is a P-glycoprotein pump inhibitor that the company says can enable oral administration of cytotoxic agents that otherwise can only be injected.

The phase III study KX-Orax-001 pitted Oraxol against intravenous paclitaxel. Data at last year's SABCS showed that the median overall survival in the modified intent to treat population was 23.3 months for Oraxol versus 16.3 months for IV paclitaxel (p=0.026). Median progression-free survival was 8.4 months for Oraxol versus 7.4 months with IV paclitaxel (p=0.023).

Oraxol was associated with a lower incidence of neuropathy and alopecia but a higher incidence of infections, low-grade gastrointestinal adverse events and grade 4 neutropenia compared with IV paclitaxel. The gastrointestinal adverse events improved in the Oraxol arm with prophylactic pre-medications.

Athenex is developing Oraxol in a number of other settings, including in combination with Glaxo's dostarlimab in neoadjuvant breast cancer, in the charity-sponsored I-Spy 2 study.

Sticking with breast cancer, Keytruda is up before an advisory committee meeting on February 9 as a neoadjuvant therapy in combination with chemotherapy, and as a monotherapy in the adjuvant setting, in triple-negative disease.

The filing is based on the Keynote-522 study and approval in the adjuvant setting, the bigger opportunity, would give Merck an edge over Roche's Tecentriq (*The year immuno-oncology could break into perioperative settings, January 25, 2021*).

Oncology aside

Elsewhere, Sarepta hopes that its third exon skipper will get FDA approval. Casimersen is intended for Duchenne muscular dystrophy (DMD) patients with genetic mutations that are amenable to skipping exon 45 of the dystrophin gene.

An interim analysis of the casimersen arm of the phase III Essence study showed a mean dystrophin protein increase of 1.736% versus 0.925% at baseline, with all 22 treated patients responding.

Casimersen appears to have cleared the regulatory precedent set by Sarepta's two other exon skippers, Exondys 51 and Vyondys 53, which demonstrated dystrophin expression levels of around 1%. However those accelerated approvals were marred by controversy, and Exondys 51 and Vyondys 53 have yet to prove themselves in confirmatory trials *(Internal FDA documents reveal a familiar story for Sarepta, January 22, 2020).*

Around 8% of DMD patients are amenable to exon 45 skipping; together, Sarepta's three exon skippers could address around 30% of the DMD market. In the long run gene therapies might displace the need for exon skippers, but here Pfizer could have the upper hand, with Sarepta's SRP-9001 recently failing in phase II *(Gene therapy trial fails to rectify Sarepta's sorry record, January 8, 2021).*

The tables below list first-time and supplementary US approvals and advisory meetings due next month, with consensus forecasts from *EvaluatePharma*.

Notable first-time US approval decisions due in February				
Project	**Company**	**PDUFA date**	**2026e sales by indication ($m)**	**Note**
StrataGraft	Mallinckrodt	Feb 2	59	Regenerative skin tissue therapy intended for adults with deep partial-thickness thermal burns
Evinacumab	Sanofi/Regeneron	Feb 11	-	Anti-ANGPTL 3 MAb for homozygous familial hypercholesterolaemia
Trilaciclib	G1 Therapeutics	Feb 15	583	Myelopreservation in patients with SCLC
Umbralisib	TG Therapeutics	Feb 15	254	See text
Amondys 45 (casimersen)	Sarepta	Feb 25	205	See text
Oraxol (oral paclitaxel)	Athenex	Feb 28	781	See text
Ygalo (melflufen)	Oncopeptide	Feb 28	474	Triple-class refractory multiple myeloma, filed on pivotal Ph2 Horizon (in combo with dexamethasone), ongoing Ph3 Ocean planned to serve as confirmatory study
Defencath/Neutrolin	Cormedix	Feb 28	230	Catheter lock solution
Dostarlimab	Glaxosmithkline	H1	582	Decision delayed from 2020 to H1 by Covid-19 travel restrictions preventing manufacturing inspection, in dMMR/MSI-H recurrent endometrial cancer
Rolontis	Spectrum	No new date provided	344	Deferred in October 2020
DaxibotulinumtoxinA	Revance	No new date provided	313	Deferred in November 2020
Liso-cel	Bristol Myers Squibb	No new date provided	1,111	Deferred in November 2020
Source: EvaluatePharma & company releases.				

Advisory committee meetings in February				
Product	**Company**	**Adcom date**	**2026e sales by indication ($m)**	**Note**
Keytruda	Merck & Co	Feb 9	4,347*	High-risk, early-stage triple-negative breast cancer, in combination with chemotherapy as neoadjuvant treatment, then as a single agent as adjuvant treatment (Keynote-522)
**SBI includes its approved use in combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumours express PD-L1. Source: EvaluatePharma & company releases.*				

Supplementary and other notable approval decisions in February			
Product	**Company**	**Indication (clinical trial)**	**Date**
Gocovri	Adamas	Off episodes in Parkinson's disease patients receiving levodopa-based therapy	Feb 1
Plegridy (intramuscular)	Biogen	Relapsing-remitting MS	Est Feb 22
Libtayo	Sanofi/Regeneron	NSCLC with ≥50% PD-L1 expression (Empower-Lung-1)	Feb 28
Vazalore	PLx Pharma	Liquid-filled aspirin capsule (325mg and 81mg doses)	End of Feb
Entresto	Novartis	Heart failure with preserved ejection fraction (Paragon HF)	Q1 (received a positive adcom in Dec)
Source: EvaluatePharma & company releases.			