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Clinical data focus for the smallest players

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Our final look at upcoming catalysts sees data expected from Replimune, TCR2 Therapeutics, Anavex and more.

After delving into the key catalysts due for big pharma and biotech companies, here *Evaluate Vantage* looks at the smallest players - those with a market cap of under $1bn. Novel approaches in oncology are one focus, while underserved neurological conditions such as Rett and Angelman syndromes are another area of interest.

Notably, almost half of the companies in this list have gone public in the past two years, and the upcoming clinical readouts will provide investors with initial glimpses at whether their money was well spent.

One such company is **Replimune**, which completed its $101m IPO in 2018. Towards the end of this year investors will see early data from two of its oncolytic immunotherapies.

RP1, the company's lead project, is a version of HSV type 1 engineered to replicate in tumours. RP1 is armed with two genes, one encoding a fusogenic protein to enhance cell death and the other encoding GM-CSF, a cytokine believed to aid immune activation. **RP2** is a derivative of RP1 that expresses an anti-CTLA-4 antibody-like molecule.

Updated results are due from a phase II study testing RP1 and Opdivo. Earlier data from skin cancer expansion cohorts were encouraging, albeit in a small number of patients with relatively short follow-up. An objective response rate of 86% was seen in cutaneous squamous cell carcinoma, comprising four complete and two partial responses, and an ORR of 31% occurred in anti-PD-1-refractory cutaneous melanoma.

As for **RP2**, initial data are expected from a phase I study in solid tumours, testing the compound as a single agent and combination with Opdivo.

Another early-stage oncology player due to report data is **TCR2 Therapeutics**, which floated last year raising $75m. TCR2 has a T-cell receptor fusion construct (TRuC)-T technology that it claimns incorporates features of Car-T and TCR T-cell therapies.

TC-210 is the company's most advanced project and targets mesothelin-positive solid tumours. A dose-escalation update from its phase I study is due. Interim data previously reported on five patients showed all to have tumour regression, including two with partial response, one of which was confirmed.

TC-110, meanwhile, targets CD19-positive B-cell haematological malignancies, and initial data are expected from a study including adult ALL and indolent non-Hodgkin's lymphoma, areas in which Car-T therapies are not currently commercialised.

Rare disease

Neurology also looks to be an area of interest for the smallest players. Rett syndrome is a rare neurological disorder that almost exclusively affects girls and is a target for **Anavex**'s therapy **Anavex 2-73**. Results from two phase II studies of the small-molecule activator of the sigma-1 receptor, one taking place in the US and the other in Australia, are due to report.

Earlier data from the open-label portion of the US study showed improvements in scores on both the Rett syndrome behaviour questionnaire and the clinical global impression-improvement scale at seven weeks in six adult patients. The upcoming data are from 15 patients in the placebo-controlled part of the trial.

There are no approved products for Rett and the failure of Newron's pivotal study in May left a thin pipeline, with Avanex one of the most advanced of those still standing. The ultimate treatment goal would be a disease-modifying approach, but this are still some way off. Novartis's gene therapy AVXS-201 is not expected to start trials until 2024.

Anavex 2-73 is also being tested in Parkinson's disease dementia. The 120-patient study is measuring two different doses versus placebo. Primary and secondary endpoints will assess cognition and parkinsonian motor symptoms and sleep function during the 14-week study.

Another condition with a lack of treatment options is Angelman syndrome, a complex genetic disorder that primarily affects the nervous system. The most advanced clinical candidate is **Ovid's OV101**, also known as gaboxadol.

The primary endpoint of the pivotal Neptune study of OV101 is CGI-I-AS, a clinical global impression improvement score at 12 weeks, with the study 95% powered to show a 0.8-point improvement from baseline on the aggregate measure of these scores.

Despite meeting the CGI endpoint in the phase II Stars trial, OV101 failed to show a benefit on a huge list of other measures. Although not detailed, younger patients responded better in the Stars study − enrolment included those aged 13-49. Neptune has enrolled patients 4-12 years old.

Other therapies in development for Angelman include Roche's RG6091, which recently started phase I, and Genetx/Ultragenyx's GTX-102, on which phase I/II data are expected next year. Both are trying to target the underlying genetic cause of the disease.

The following table notes additional fourth-quarter events for the smallest companies and includes consensus forecasts from *EvaluatePharma*. *Evaluate Vantage* has separately assessed expected catalysts for larger drug makers, and biotech companies with a market cap over $1bn.

Selected Q4 events (excludes Covid-19 data)					
Project	**Company**	**Therapy area**	**Q4 event**	**2026e indication sales ($m)**	**Note/*Vantage* coverage**
HMI-102	Homology	Phenylketonuria	Ph1/2 Phenix update due, delayed by Covid-19, specific guidance on timing not provided	884	Gene therapy; dosing Biomarin's BMN 307 recently started
AXO-Lenti-PD	Axovant	Parkinson's disease	6-mth data from second dose cohort of Sunrise-PD study (Ph1/2)	732	Encouraging data in first cohort; second dose is ~threefold higher
Edasalonexent	Catabasis	DMD	Topline ph3 PolarisDMD	653	Ph2 failed on primary that measured muscle composition and inflammation - shares tanked 71%, Ph3 has a different endpoint
					Ph2b Nefecon produced significant

Selected Q4 events (excludes Covid-19 data)					
Nefecon (budesonide)	Calliditas	Chronic autoimmune kidney disease IgA nephropathy	Ph3 NeflgArd study	591	significant reductions in proteinuria and stabilised kidney function, *Hope on the horizon for rare kidney disease*
KVD900	Kalvista	HAE	Ph 2	561	Oral plasma kallikrein inhibitor in acute HAE rescue therapy, market largely consists of IV or SC treatments
RP1	Replimune	Cutaneous squamous cell carcinoma, melanoma & non-melanoma skin cancer	Ph1b Artacus study, updated data from Ph2 RP1 + Opdivo cohorts in melanoma and non-melanoma skin cancer	543	See text
SRK-015	Scholar Rock	Type 2 and Type 3 Spinal muscular atrophy	Topaz Ph2	502	54 patients who have progressed through at >6mth, anti-myostatin MAb
Graspa (eryaspase)	Erytech	Pancreatic cancer	Interim superiority analysis of Trybeca1 (final data H2 2021)	499	Ph2: eryaspase plus chemotherapy showed a 43% reduction in risk of death (p=0.034)
Nurown	Brainstorm Cell Therapeutics	ALS	Pivotal Ph3	472	Therapy from stem cells harvested from a patient's bone marrow
OV101	Ovid Therapeutics	Angelman syndrome	Pivotal Neptune	432	See text
TC-210	TCR2 Therapeutics	Mesothelin-expressing solid tumors	Interim update from ph1 portion of the ph1/2	382	See text
CB-839 (telaglenastat)	Calithera	Metastatic renal cell carcinoma	Ph2 Cantata (late Q4/early 2021)	380	Telaglenastat + Cabometyx vs Cabometyx, study powered to detect 31% improvement over the 8mth PFS in the control
Plinabulin	Beyondspring	Chemotherapy-induced neutropenia	CIN: final data for Protective-2, NDA submission	206	Interim data: Neulasta combo improved Gr4 neutropenia prevention vs Neulasta alone (p<0.01)
					Interim Edge data: IGF-1 levels

Selected Q4 events (excludes Covid-19 data)					
					data. IGF-1 levels were maintained
CRN00808/ paltusotine	Crinetics Pharmaceuticals	Acromegaly	Ph2 Acrobat Evolve (full responder) and Acrobat Edge (partial responder)	129	when switching to oral paltusotine from depot injections of somatostatin receptor ligands
AGTC-501	Applied Genetic Technologies	X-linked retinitis pigmentosa	Ph1/2	118	Gene therapy, interim analysis for groups 5 and 6 to evaluate safety and efficacy at higher doses
Anavex 2-73 (blarcamesine)	Anavex	Rett Syndrome, Parkinson's disease	US ph2 study, Ph2 Avatar (Australian), ph2 Parkinson's disease dementia	114	See text
TC-110	TCR2 Therapeutics	CD19+ r/r NHL or adult ALL	Interim data from Ph1 portion of the ph1/2	80	See text
AXO-AAV-GM1	Axovant	GM1 gangliosidosis	6 month data from low dose cohort of stage 1 of registrational ph1/2	59	Current treatment options are symptomatic and supportive; AXO-AAV-GM1 is a gene therapy
Eprenetapopt (APR-246)	Aprea	Front-line TP53 mutant myelodysplastic syndromes	Ph3, in combination with azacitidine	27	Small molecule that reactivates mutant and inactivated p53 protein
RP2	Replimune	Sold tumours	Ph1 RP2 single-agent and combination with Opdivo	-	See text
IMR-687	Imara/ Lundbeck	Sickle cell anaemia	Topline ph2a data	-	Early data: 1.7% mean increase in fetal haemoglobin from baseline at 25wk for a high dose (no increase for placebo or a low-dose cohort)
Pegunigalsidase alfa/ PRX –102	Protalix	Fabry disease	P3 Bright	-	Four-wk dosing study, Jan Pdufa for infusion q 2wk
Sources: Sources: Evaluatepharma, clinicaltrials.gov, company releases, analyst notes					

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