Evaluate Vantage

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Snippet roundup: Astra deals with Sanofi and Juno and Accera hit trouble

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Welcome to your weekly roundup of EP Vantage's snippets – short takes on smaller news items.

This week, February 27 to March 3, 2017, we had thoughts on the following: Astra and Sanofi team up on next-gen RSV antibody; the clock starts ticking again for Dynavax; Juno makes it official: it's now in third place, behind Kite and Novartis; Accera failure is food for thought; Cynosure shareholders want Hologic deal halted; Viewray accelerates to the US; Exelixis ramps up I-O Cabo combos.

These snippets were previously published daily via twitter.

Astra and Sanofi team up on next-gen RSV antibody

March 3, 2017

Astrazeneca has turned more of its pipeline into cash, this time enlisting Sanofi to aid the development of a potential next-generation respiratory syncytial virus (RSV) antibody, MEDI8897. The deal, worth €120m ($127m) up front and up to €495m in milestones, makes more sense than the recent divestment of Zoladex, however, thanks to Sanofi's expertise in vaccines and an unmet need in RSV. MEDI8897 is designed to have a long half-life so that only one dose would be needed for the entire RSV season; if approved this should give it the edge over Astra's marketed RSV MAb, Synagis, which is injected once a month. A phase IIb study of MEDI8897 in healthy preterm infants is due to report next year, and a phase III trial in healthy full-term infants is also planned. This puts it behind Regeneron/Sanofi's suptavumab and Novavax's RSV F Vaccine, both in phase III in infants. However, a phase III study of Novavax's project in older adults failed last year.

Late stage RSV monoclonal antibodies and vaccines

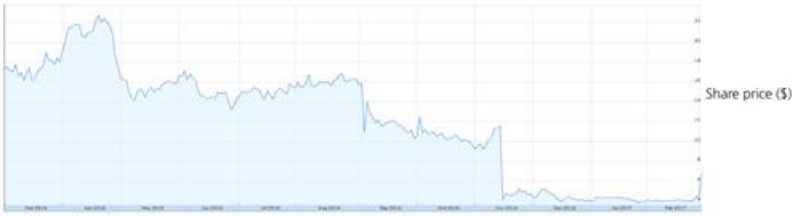
Phase	Product	Pharma class	Company	2022e WW sales ($m)
Marketed	Synagis (palivizumab)	Anti-RSV MAb	AbbVie/Astrazeneca	919
Phase III	RSV F Vaccine	RSV vaccine	Novavax	360
	Suptavumab	Anti-RSV MAb	Regeneron/Sanofi	-
	Palivizumab biosimliar	Anti-RSV MAb	Harvest Moon Pharmaceuticals	-
Phase II	MEDI8897	Anti-RSV MAb	Astrazeneca	9
	MEDI7510	RSV vaccine & TLR 4 agonist GLA-SE	Astrazeneca	-
	MVA-BN RSV	RSV vaccine	Bavarian Nordic	-
	ALX-0171	Anti-RSV MAb	Ablynx/Vectura	-
	GSK3003891A	RSV vaccine	GSK	-
	GSK3389245A	RSV vaccine	GSK	-

Source: EvaluatePharma

The clock starts ticking again for Dynavax

March 2, 2017

The wait is on for Dynavax and Heplisav B – yet again. The FDA has given itself another six months to review further information submitted to support the company's hepatitis B vaccine, in response to a November complete response letter (CRL). The fact that the company managed to satisfy the regulator with its response so swiftly can perhaps be interpreted positively. Some investors thought so – the stock advanced 53% yesterday, although it remains close to eight-year lows. But with concerns ranging from immunogenicity to a cardiac signal, a positive outcome is far from assured, and a second advisory committee panel before the August PDUFA date is not out of the question. The FDA's concerns about this asset have now spanned almost a decade, manifesting in a clinical hold back in 2008 and two CRLs. The company's pivot earlier this year to immuno-oncology research suggests that this really is the last push for Heplisav-B, and few will likely rue the end to this tainted project.



Dynavax 12 month share price

Juno makes it official: it's now in third place, behind Kite and Novartis

March 2, 2017

Juno's 8% fall this morning, following yesterday's discontinuation of its lead, JCAR015, only makes sense given the strange run-up the stock had enjoyed into the positive read-out of Kite's competing Zuma-1 trial of KTE-C19. After all, with several patient deaths due to cerebral oedema under its belt, and the pivotal Rocket trial in childhood leukaemia on hold, the writing for JCAR015 had been on the wall since November. Juno is fortunate in being able to pivot to JCAR017, an anti-CD19 CAR that could be superior thanks to using a defined cell composition. However, in its lead lymphoma indication JCAR017 is behind both KTE-C19 and Novartis's CTL019, and even Juno's plan to have it filed in late 2018 sounds highly optimistic. For now the company says it first needs to decide which of two doses to take forward, based on further data from the phase I Transcend trial. It will then look at starting a registrational lymphoma study "later this year", its chief executive, Hans Bishop, said yesterday. At a time when the market wants some certainty such vagueness is unlikely to help Juno.

CD19 CAR-T timeline in lymphoma

Project	Company	Academic source	Cells used	Study	Trial ID	Timing
KTE-C19	Kite	NCI/Zelig Eshhar	PBMCs	Zuma-1 (registrational)	NCT02348216	Positive 6mth follow-up data reported; rolling BLA to be completed Q1 2017
CTL019	Novartis	Uni of Pennsylvania	PBMCs	Juliet (registrational)	NCT02445248	3mth follow-up data Q2 2017; filings Q4 2017
JCAR017	Juno	Seattle Children's	1:1 ratio of CD4/CD8	Transcend	NCT02631044	Early data at Ash 2016; registrational trial to begin "later in 2017", filing in 2018/19

Accera failure is food for thought

March 1, 2017

The amyloid theory of Alzheimer's disease is not the only hypothesis to have evidence against it. The failure in phase III of Accera's AC-1204 is a blow to a concept that relies on providing an alternative energy source, ketones, to damaged brain cells that cannot metabolise glucose. In the Nourish study in 400 patients with mild to moderate Alzheimer's, AC-1204 did not beat placebo as measured by improvement on the Adas-Cog test. Accera is blaming the failure on a formulation change between successful phase II trials and Nourish, saying the new concoction "had the unintended consequence" of producing lower drug plasma levels than the version used in phase II. Full Nourish data will be released at the Alzheimer's Association International Conference in London in July. Showing the optimism necessary among Alzheimer's drug developers, Accera now has a new formula that it believes will boost AC-1204 levels – but securing funding for further trials will surely be tricky.

Phase III trials in Alzheimer's diease

Project	Company	Type/entry criteria	Trial name	NCT ID	Date
Nilvadipine/ ARC029	Archer	mild to mod (MMSE >12), stable (>3 mos) on AChEi or memantine	Nilvad	NCT02017340	Sep-16
AC-1204	Accera	mild to mod	Nourish	NCT01741194	Fail
Solanezumab	Lilly	mild (MMSE 20-26)	Expedition 3	NCT01900665	Fail
Flebogamma	Grifols	mild to mod	Ambar	NCT01561053	Dec-16
Verubecestat	Merck & Co	mild to mod, stable (>3 mos) of AChEi or memantine if taken	Epoch	NCT01739348	Fail
ALZT-OP1 (cromolyn+	AZTherapies	early, stable (>3 mos) on AChEi or memantine	Cognite	NCT02547818	Mar-18
Gantenerumab	Roche/ Morphosys	mild	-	NCT02051608	Jul-18
Azeliragon	vTv Therapeutics	mild (MMSE 21-26), stable (>3 mos) on AChEi or mematine	Steadfast	NCT02080364	Mar-18
Verubecestat	Merck & Co	prodromal, stable (>3mos) on AChEi or mematine if taken	Apecs	NCT01953601	Jul-19
AZD3293/LY3314814	AstraZeneca/ Lilly	Early (MMSE 20-30)	Amaranth	NCT02245737	Aug-19
Aducanumab*	Biogen	mild (MMSE 24-30), stable (>2 mos) on AChEi or mematine	Engage & Emerge	NCT02477800 & NCT02484547	Feb-20
Crenezumab	Roche	prodromal to mild (MMSE >22)	CREAD1	NCT02670083	Aug-20
Crenezumab	Roche	prodromal to mild	CREAD2		Yet to start
CNP520 or CAD106**	Amgen/ Novartis	Risk for the onset of AD	Generation	NCT02565511	Aug-23
INI-54861911	J&J	asymptomatic, at risk of AD	Early	NCT02569398	Apr-23

*Notes: Excludes programmes for non-cognitive aspects of condition, such as agitation; *two identical studies; **two agents tested separately in one study.*

Cynosure shareholders want Hologic deal halted

February 28, 2017

Abbott's purchase of Alere is not the only medtech megamerger to run into trouble. In that case it is the buyer that is seeking to back out of the transaction, but in the case of Hologic and Cynosure it is the merger's target. Shareholders in Cynosure, which makes laser-based technologies designed to burn fat or remove hair, scars or tattoos, have filed a class action suit to halt the company's proposed $1.4bn sale to Hologic. The investors claim that they do not have enough information to ensure that the cash purchase is a good deal, alleging that the SEC filing in which Cynosure recommended the transaction is missing vital information about forecast financials. Neither did the filing disclose whether an unnamed bidder competing with Hologic had signed a confidentiality agreement, and if so, whether that agreement precludes the bidder from topping Hologic's offer, the investors said. Lastly the shareholders take issue with what they say are disproportionate benefits to Cynosure insiders, and allege that its chief executive, Michael Davin, will receive a payoff of more than $30m.

Viewray accelerates to the US

February 28, 2017

The world's first commercial system combining MRI imaging with a compact linear accelerator "will lead to a new standard of care in radiation oncology", says its developer, Cleveland, Ohio-based Viewray. The MRIdian Linac, a linear accelerator-based, MRI-guided radiation therapy system, gained FDA 510(k) clearance, pushing Viewray's shares up 20% on Nasdaq. The system will find a market niche, the company believes, because tumours and organs move and change shape during the course of radiation treatment, meaning simultaneous imaging allows more targeted therapy. Whether this approach will in fact become the standard is debateable, but it has seen some commercial success in Europe, with the group receiving 13 new orders worth $77m last year since approval in September. The US market entry will come as a relief to Viewray's investors, who have pumped more than $140m into the group's five venture rounds over the last decade. The company has also closed two PIPE deals worth $40m since it went public on the OTC Markets via a reverse merger in July 2015. It uplisted to Nasdaq last March.

ViewRay's funding to date

Date	Financing Round	Investment ($m)	Investor Name
January 18, 2017	Private Investment in Public Equity (PIPE)	26.1	Puissance Capital, Acuta Capital Partners, Kearny Venture Partners, OrbiMed Advisors
August 19, 2016	Private Investment in Public Equity (PIPE)	13.8	OrbiMed Advisors, Xeraya Capital, Kearny Venture Partners, CRG
March 4, 2015	Series E	15.0	Undisclosed Investors
December 17, 2013	Series D (third close)	30.0	Aisling Capital, Cowealth Medical Holding, F-Prime Capital, Kearny Venture Partners, OrbiMed Advisors
May 21, 2013	Series D (second close)	15.0	Aisling Capital, F-Prime Capital, Kearny Venture Partners, OrbiMed Advisors, Siemens Venture Capital
February 18, 2013	Series D	10.9	Undisclosed Investors
March 13, 2012	Series C	45.0	Siemens Venture Capital, Aisling Capital, F-Prime Capital, Kearny Venture Partners, OrbiMed Advisors
April 14, 2009	Series B (second close)	15.0	OrbiMed Advisors, F-Prime Capital, Aisling Capital, Kearny Venture Partners
January 21, 2008	Series B	10.0	OrbiMed Advisors, F-Prime Capital, Aisling Capital, Kearny Venture Partners
-	Series A	3.0	Undisclosed Investors
Total		183.7	

Source: EvaluateMedTech

Exelixis ramps up I-O Cabo combos

February 28, 2017

Exelixis is eyeing a first-line indication for its renal cell carcinoma therapy Cabometyx – but it is already looking beyond this with new immuno-oncology collaborations with Bristol-Myers Squibb and Roche. The agreement with Bristol will see the companies co-fund a pivotal trial of Cabometyx plus Opdivo, either with or without Yervoy, in first-line RCC. Exelixis could pay as little as 20-25% of the trial costs, Leerink analysts estimate, also taking into account contributions from other partners Ipsen and possibly Takeda. Meanwhile, Roche will provide its PD-L1 inhibitor Tecentriq for Exelixis to carry out a dose-escalation study in locally advanced or metastatic solid tumours. At this year's JP Morgan meeting, Exelixis's chief executive, Mike Morrissey, highlighted the importance of PD-(L)1 combos for the "next wave of potential indications" for Cabometyx, identifying lung, liver and triple-negative breast cancers as other possible uses. And there could be more deals to come, he told *EP Vantage*: "Not only are we agnostic, we're looking to get as much traction with as many of those combinations as possible." Meanwhile, Exelixis plans to submit a supplemental NDA for Cabometyx in first-line RCC in the third quarter, and will also report topline data from the phase III Celestial trial in hepatocellular carcinoma this year.

Cabometyx's new PD-(L)1 combo trials

Partner	Combination	Trial details	Notes
Bristol-Myers Squibb	Cabometyx + Opdivo +/- Yervoy	Phase III trial in first-line RCC; trials planned in bladder cancer, HCC & and potentially other tumour types	Co-funded, Ipsen participating, to start in H1 2017
Roche	Cabometyx + Tecentriq	Phase 1b dose escalation study in locally advanced/ metastatic solid tumours	Exelixis-sponsored, Ipsen to pay 35%, to start mid-2017

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