Evaluate Vantage

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Ash 2019 preview – the first winner and losers emerge

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Celgene's registrational Transcend NHL-001 study will be a big story at Ash, but the early focus falls on what has not been presented.

For biotech followers yesterday's unveiling of presentations at the upcoming Ash conference was notable for prompting the deflation of the bubble around next-generation BTK inhibitors: Arqule and Sunesis both fell heavily. Constellation was the unexpected winner, up 90% on very early data with its BET inhibitor in first-line myelofibrosis.

Of course, the meeting – the year's last big medical showdown – is crucial for some bigger companies too, though this might not be reflected in their stock movements. For instance, liso-cel's registrational study is hugely relevant to the contingent value right (CVR) payable under Bristol-Myers Squibb's takeout of Celgene.

One of the events on which this CVR's payout depends is the US approval of liso-cel (JCAR017) for lymphoma by the end of 2020. Celgene has vowed to file the Car-T project with the FDA by the end of this year, and Ash will allow investors the first look at Transcend NHL-001, the study on which this hinges, for over a year.

If deaths prior to infusion and manufacturing failures are excluded liso-cel's Ash abstract reveals a 73% ORR, broadly in line with Gilead and Novartis's marketed Car-T therapies Yescarta and Kymriah. With these other Car-T therapies available, however, a key doubt is whether the FDA will even approve a third without significantly stronger data.

A key focus will thus fall on safety, and here liso-cel looks good, with only a 2% rate of serious cytokine release syndrome, for instance. But four treatment-related deaths will no doubt draw attention; at the last significant update there had been one.

BCMA... again

Among other Celgene assets, few investors are paying attention to the anti-BCMA bispecific CC-93269, and might be impressed by its first clinical data due at Ash. The meeting will feature over 25 different BCMA-targeting assets, and the crowding of this space has already led to the discontinuation of Autolus's Auto2, for instance.

Also closely watched is Glaxosmithkline's belantamab mafodotin, whose Dreamm-2 study has been submitted for an Ash late-breaker. Bluebird's BCMA presence centres on an underwhelming update for bb21217; its lead

asset, ide-cel (bb2121), forms another part of the Celgene CVR, but its pivotal KarMMa study did not make it into Ash, and is expected instead to be unveiled in a press release.

Selected Ash 2019 presentations*				
Project	**Company**	**Abstract data**	**Note**	**Ash abstract**
Adoptive cell therapy				
Liso-cel (JCAR017)	Celgene	Transcend NHL-001: 73% ORR, mPFS 6.8mth, mOS 19.9mth; 26 manu failures, 4 treatment-related deaths	CVR depends on US DLBCL approval by 31 Dec 2020	241
Liso-cel (JCAR017)	Celgene	Transcend CLL-004: 82% ORR	Possible additional use with no current Car-T therapies	503
NY-ESO-1 TCR-T	Tmunity	2 evaluable: 1 SD	First clinical data with Crispr-edited eTCR	49
Anti-BCMA therapies				
CC-93269	Celgene	12 evaluable at ≥ 6mg: 83% ORR	First human data for this bispecific	143
JNJ-68284528	J&J	21 evaluable: 90% ORR, 29% CR	Caritude-1 study	577
LCAR-B38M	Legend	74 evaluable: 88% ORR, 74% CR; mPFS 20mth	Compare vs JNJ-68284528, which uses different manufacturing	579
bb21217	Bluebird	18 evaluable: 83% ORR, but 6 relapsed	No significant update for ide-cel	927
Sickle cell disease				
Lentiglobin	Bluebird	Little new in abstract with 7 Mar 2019 cutoff.	Placeholder abstract?	990
ST-400	Sangamo/Sanofi	3 treated, 1 serious AE	Early data likely do not challenge Lentiglobin	3544
BTK inhibition				
ARQ 531	Arqule	6 PRs in 22 C481Smut subjects	EHA update saw responses in 4/6 C481Smut subjects	4298
Loxo-305	Lilly (ex Loxo/Redx)	1 PR & 4 PR-L** in 5 CLL subjects (1 with C481Smut)	First human data	501
Vecabrutinib	Sunesis	27 now treated (12 with C481Smut) at up to 300mg bid; no responses	Placeholder abstract?	3041
Calquence	Astrazeneca	30mth PFS 90% for Gazyva combo, 82% for Calquence monotherapy, 34% for Gazyva + chemo	Elevate-TN: 1st-line CLL	31
Anti-CD20 bispecifics				
Mosunetuzumab	Roche	Various ORR analyses in r/r NHL		1285
REGN1979	Regeneron	45 DLBCL subjects evaluable: 33% ORR across all doses		762

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XmAb13676	Xencor	ORR 33% (6/18) in r/r NHL 20% (1/5) in CLL		4079
GEN3013	Genmab	"Evidence of clinical activity"	Placeholder abstract?	758
Other				
CPI-0610	Constellation	4/4 subjects had ≥35% SVR & ≥50% improvement in TSS	V early 1st-line myelofibrosis data	4164
AMT-061	Uniqure	52-week update for Padua variant project	Possibly the first haemophilia B gene therapy	3348
Polivy	Roche	46 evaluable FL subjects: 76-83% ORR	Gazyva + Revlimid combo; approved as Rituxan combo	126
IMGN632	Immunogen	ORR 17% (11/66) in AML, 43% (3/7) in BPDCN	Optioned to Jazz (IMGN779, earlier optioned, now discontinued)	734
*Note: *excludes late-breakers, which are expected to include Dreamm-2 study of Glaxo's anti-BCMA ACD belantamab mafodotin; **partial remission with lymphocytosis (technically not PR).*				

It was the absence of data that sent down the two non-covalent BTK inhibitor players yesterday. Sunesis fell 23% on news that its vecabrutinib has yet to generate a single remission, so investors must hope that the Ash abstract is a placeholder, with more data at the meeting itself.

Arqule, off 18%, failed to convince with ARQ 531, while Lilly provided the first early signs of activity with its Redx-originated, Loxo-derived asset, Loxo-305. The most closely watched Ash-relevant BTK inhibitor could actually be Astrazeneca's Calquence, whose first-line Elevate-TN trial marks a serious challenge against Abbvie's Imbruvica in first-line CLL.

Away from oncology Bluebird also features, courtesy of Lentiglobin data from the HGB-206 sickle cell trial, but the main point will be that Sanofi/Sangamo's ST-400 does not look like a threat, at least not yet. There is no Ash presentation from another sickle cell challenger, Vertex/Crispr's CTX001.

Also not present are any clinical data for Fate Therapeutics' stem cell-derived NK cell therapies FT500 or FT516; this disappointment sending down the originator's stock 15% yesterday.

But what about the early winner of Ash? Constellation is a thinly traded biotech that floated just over a year ago, but its lead asset, CPI-0610, has impressed. The Ash abstract covering this BET inhibitor details its combination with Incyte's Jakafi in untreated myelofibrosis, but concerns only four subjects given at least four treatment cycles.

True, all four exceeded thresholds for spleen volume reduction and total symptom score improvement. But, a day after Nextcure surged 249%, perhaps Constellation's 90% stock increase is another indication of biotech investors' thirst for glimmers of efficacy, however early these might be.

The Ash conference takes place in Orlando, Florida on December 7-10.

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