

ASCO 2017

Conference report

Highlights from the ASCO Annual Meeting

Pharma & biotech

21 June 2017

Edison attended the 2017 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago, US, on 2-6 June. This year the main focus was chimeric antigen receptor (CAR) T Cell therapies, in particular CARTs targeting BCMA from Bluebird Bio and Nanjing Legend; and immuno-oncology (IO) combinations such as IDO1/PD-1 inhibitors and new targets like LAG3 and GITR. Targeted therapies also took centre stage, particularly Loxo's larotrectinib and AstraZeneca's Lynparza, along with Roche's APHINITY data. Finally, we also present data from companies under our coverage: Hutchison China MediTech, MorphoSys, PharmaMar, Prima Biomed and Viralytics.

CARTs getting ready for prime time

With impressive responses seen in haematological cancers with CD19 CARTs, this year the focus was on new targets such as the B-cell maturation antigen (BCMA). Data on anti-BCMA CARTs from Bluebird Bio and Nanjing Legend in relapsed, refractory multiple myeloma showed overall response rates (ORR) of 89% and 100%, respectively, with a manageable safety profile. CARTs are seen more and more as a viable commercial product that hold significant upside as new data are generated, manufacturing is streamlined and the possibility to treat earlier lines becomes apparent.

Focus shift to new immuno-oncology combinations

Incyte presented updated data of its IDO inhibitor epacadostat in combination with Keytruda (pembrolizumab, anti-PD-1) in lung cancer. Two previous partial responses (PR) turned into complete responses (CR); however, due to the small size and uncontrolled design of the trial it is difficult to assess the synergy between both products. Bristol-Myers Squibb (BMS) presented initial efficacy data of a combination of an anti-LAG3 antibody with Opdivo (nivolumab) and preliminary data of its anti-GITR antibody also in combination with Opdivo.

Targeted therapies also in the spotlight

Loxo Oncology's larotrectinib impressed with 76% ORR in patients with the rare TRK fusion mutation. AstraZeneca's PARP inhibitor Lynparza showed positive data in patients with HER2-negative BRCA mutated metastatic breast cancer (BC); patients experienced c 60% ORR, doubling the ORR of the chemotherapy arm. These data strengthen the company's oncology franchise. Data from Roche's APHINITY study, in which adding Perjeta to Herceptin improved overall survival in BC patients by just 0.9%, was seen as positive for competitor Puma Biotech.

A flurry of data from our coverage universe

We attended all presentations from companies under our coverage: Chi-Med's fruquintinib Phase III data (FRESCO); MorphoSys' MOR202 and MOR208; PharmaMar's lurbinectedin data in endometrial cancer, which warrant further development; Prima Biomed's combination of IMP321 and chemotherapy; and Viralytics' combination of oncolytic virus Cavatak with Yervoy (ipilimumab) in patients who have failed anti-PD-1 therapy.

Companies in this report

AstraZeneca
Bluebird Bio
Bristol-Myers Squibb
Hutchison China MediTech*
Incyte
Juno Therapeutics
Kite Pharma
Loxo Oncology
Merck & Co
MorphoSys*
Nanjing Legend
Novartis
PharmaMar*
Prima Biomed*
Puma Biotechnology
Roche
Viralytics*

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CAR-Ts take the spotlight

New and updated data on BCMA target

Therapies based on chimeric antigen receptor (CAR) T cells have garnered enormous attention due to impressive response rates in heavily treated blood cancer patients. Most CART players have focused on the CD19 receptor, which is expressed in B-cell malignancies, including many leukaemias and lymphomas. At ASCO new and updated data were presented from two CARTs directed towards a different target, the B-cell maturation antigen, or BCMA, which is implicated in leukaemia, lymphoma and multiple myeloma. Bluebird Bio and Nanjing Legend presented clinical data in relapsed, refractory multiple myeloma (r/r MM). Bluebird's bb2121 achieved an 89% ORR with four CRs; grade 1 or 2 cytokine release syndrome (CRS) was observed in 73% of patients (abstract [3010](#)). Nanjing Legend's LCAR-B38M yielded an impressive 100% ORR with 14 CR with 85% of patients experiencing CRS, but manageable and mostly grade 1 or 2 ([LBA3001](#)). We compare them with previously reported data from Novartis in Exhibit 1.

Exhibit 1: Comparison of anti-BCMA therapies				
	Bluebird	Nanjing Legend	Novartis	
First reported	ASCO 2017	ASCO 2017	ASH 2016	
Construct	Lenti/mscFv-4-1-BB-z	Lenti/?tbc-4-1-BB-z	Lenti/hscFv-41-BB-z	
Therapy	bb2121	LCAR-B38M	CART-BCMA	
Sites	Multicentre, US	Multicentre, China	Single centre, Penn	
Antigen cut-off	50%	50%	None	
Prior lines (median)	≥3 (7)	>3 (4)	≥3 (9)	
Conditioning	Flu/Cy	Flu/Cy	None or Cy	
Responses	ORR 89%, n=18, 4 CR	ORR 100%, n=19, 14 sCR	ORR 44%, n=9, 1 sCR	
Safety	71% CRS	85% CRS	89% CRS and 1 DLT	

Source: Edison Investment Research, Bluebird bio, Nanjing Legend and Novartis. Note: ORR: overall response rate; CR: complete response; sCR: stringent complete response; CRS: cytokine release syndrome; Flu: fludarabine; Cy: cyclophosphamide; DLT: dose-limiting toxicity.

Differences across studies may be related to the different population setting and number of prior lines of therapy. Patients in the Bluebird study had a median of seven lines, while Legend patients had a median of just four lines. The higher efficacy seen in Bluebird's and Legend's products vs Novartis may be associated with the level of antigen expression; in Bluebird's and Legend's trials a 50% cut-off was necessary, while the Novartis trial did not require expression of BCMA. Nanjing Legend will need to run a US and/or EU trial to be considered a firm competitor for Bluebird and Novartis. We believe that these results validate BCMA as a target in r/r MM.

CAR-T race reaching the finish line – Juno's comeback

CAR-Ts are approaching the market, with Novartis's CTL019 (tisagenlecleucel) leading the race. A biologics license application (BLA) in r/r paediatric and young adult patients with B-cell acute lymphoblastic leukaemia (ALL) was accepted and granted priority review by the FDA on 29 March 2017. The FDA is expected to take action within six months of the application, ie before 29 September 2017. An advisory panel will discuss the application on 12 July 2017. Close behind is Kite Pharma's KTE-C19 (axicabtagene ciloleucel), also with priority review and approval decision date on 29 November 2017 for relapsed, refractory diffuse large B-cell lymphoma (r/r DLBCL).

Competitor Juno Therapeutics suffered a setback last year when it announced the discontinuation of JCAR015 due to patient deaths. Although in third position, the company is back in the race with [new data](#) on JCAR017 (also a CAR-T against CD19 antigen, but with a different construct) from the TRANSCEND study presented at ASCO. In 41 patients with r/r DLBCL the CR rate at three months was 39% and ORR was 51% across dose levels. 35% of patients reported severe cytokine release syndrome. There were no deaths related to either of these side effects. One patient died from

respiratory failure deemed related to chemo pre-treatment and JCAR017. Therefore, although the company has generated comparable data to its competitors, it is still well behind them and we expect it to remain in the third position.

For the sake of comparison, Kite's KTE-C19 data at three months from the pivotal ZUMA-1 study in 55 r/r DLBCL patients showed a CR rate of 33% and ORR of 39%. The rates of severe cytokine release syndrome and neurotoxicity were 18% and 34%. There were two patient deaths. Final six-month results in 77 r/r DLBCL patients showed a CR rate of 31% and 36% ORR. The rate of severe cytokine release syndrome was 13%. Both CRS and neurologic events were generally reversible.

We are including Novartis's three-month data recently presented at the International Conference on Malignant Lymphoma (ICML) on 14 June 2017. Of note, c 40% of subjects (42 of 121) discontinued before being treated with CTL019 due to disease progression or worsening of their clinical status, which may have been caused by the trial design, which delayed infusion after apheresis, according to the presenter. In 51 r/r DLBCL patients the CR rate was 37% and ORR was 45%. The rates of severe cytokine release syndrome and neurotoxicity were 26% and 13%, respectively. The remission data are comparable across the three studies.

Exhibit 2: Comparison across trials

	TRANSCEND			ZUMA-1			JULIET		
	# of patients	ORR	CR	# of patients	ORR	CR	# of patients	ORR	CR
3 months	41	51%	39%	55	39%	33%	51	45%	37%
6 months	N/A	N/A	N/A	77	36%	31%	N/A	N/A	N/A
Side effects	35% CRS; 35% neutropenia; 31% fatigue			18% CRS; 34% neurotoxicity at 3 months; 13% CRS at 6 months			26% CRS; 13% neurotoxicity		

Source: Edison Investment Research, Juno Therapeutics, Kite Pharma and Novartis. Note: ORR: overall response rate; CR: complete response; CRS: cytokine release syndrome.

Immuno-oncology combinations – new & updated data

Updated data on Incyte's IDO1 inhibitor plus Keytruda

Updated [results](#) were presented from a clinical trial combining Incyte's epacadostat (inhibitor of the enzyme indoleamine 2,3-dioxygenase, which allows tumour cells to evade the immune system) with Merck's anti-PD-1 antibody Keytruda in 40 patients with non-small cell lung cancer (NSCLC). The overall response rate remains at 35% as previously reported, but now two patients have a complete response, while 12 have a partial response (vs previously 14 PR). IDO inhibitors have been hailed as a potential alternative to CTLA4 in IO combinations as the only approved combination of Opdivo (anti-PD-1) and Yervoy (anti-CTLA4) carries significant toxicities. However, this is a small and uncontrolled trial; hence, it is unclear to what extent epacadostat is adding to Keytruda's efficacy.

Epacadostat and Keytruda have showed activity in renal cell carcinoma, urothelial cancer and squamous head and neck cancer. Incyte and Merck recently expanded their collaboration to include an additional seven Phase III studies of the combination in melanoma, bladder cancer, NSCLC, renal cancer and head-and-neck cancer. Incyte is running a similar program with Bristol-Myers Squibb (BMS) and its checkpoint inhibitor Opdivo.

Initial data from LAG3 and G1TR combinations with Opdivo

BMS presented initial efficacy [data](#) from a combination trial of BMS-986016 (anti-LAG3) with Opdivo in patients with melanoma that had progressed after PD-1/L1 therapy. The combination had an ORR of 12.5%; in high LAG3 expressers ORR was threefold higher. Preliminary [data](#) from a combination BMS-986156 (anti-G1TR) with Opdivo in advanced solid tumours was also presented.

Targeted therapies remain relevant

Loxo Oncology: Targeted personalised medicine

Data from three clinical trials testing larotrectinib showed a 76% ORR in patients diagnosed with 17 different types of advanced cancer harbouring a rare genetic mutation known as TRK fusion, which occurs across a wide array of cancers and is involved in activating cancer cells to grow. The responses were locally assessed only, and are subject to confirmation by independent review. Loxo would look for a US filing late this year or early 2018 if responses are confirmed. The data underscores the fact that although immunotherapies have taken the spotlight, targeted therapies are still generating positive and relevant data ([LBA2501](#)).

Lynparza: Full data from OlympiAD study presented

AstraZeneca released [full data](#) from the Phase III OlympiAD study in 302 patients with HER2-negative gBRCA-mutated metastatic breast cancer. Data showed that patients treated with Lynparza (olaparib, PARP inhibitor) had a 42% reduction in risk of their disease worsening or death compared to those who received chemotherapy. 59.9% of patients responded to treatment, more than double the 28.8% objective response rate seen in patients on chemotherapy. Moreover, the safety profile favoured Lynparza, with 37% of patients experiencing grade 3 or greater adverse events compared with 51% of patients on chemotherapy. The drug was approved for ovarian cancer in 2014 and has sold \$317m until FY16. Two other drugs, Clovis Oncology's Rubraca (rucaparib) and Tesaro's Zejula (niraparib) have recently been approved in ovarian cancer; hence, expansion to other indications will help build on its existing competitive advantage and grow its oncology franchise.

Data from APHINITY study give hopes to Puma's neratinib

Roche presented full data from the APHINITY study in nearly 5,000 women with HER2 positive breast cancer. Data showed that adding Roche's Perjeta (pertuzumab) to post-surgery treatment with Herceptin (trastuzumab, also from Roche) resulted in 19% lower risk of recurrence of invasive disease or death compared to those who were treated with Herceptin alone. However, in absolute survival benefit, 94.1% of the Perjeta/Herceptin patients were free of recurrence, compared with 93.2% in the Herceptin-only arm, which is less than 1% benefit of the combination over Herceptin alone. This was good news for competitor Puma Biotechnology as it could give its drug neratinib a chance to remain competitive in this setting; the primary analysis in the ExteNET trial showed an OS of 94.2% at 24 months. The market dynamics between both drugs will depend on pricing and how neratinib's diarrhoea side effects are managed with loperamide prophylaxis.

Updates across our coverage universe

Chi-Med: Oral presentation of fruquintinib Phase III data

Dr Jin Li presented full data from the Phase III FRESCO study in a well-attended oral presentation (abstract [3508](#)). In the trial, 416 patients with metastatic colorectal cancer (mCRC) who have failed at least two lines of systemic chemotherapy were randomised 2:1 to take fruquintinib (anti-VEGFR 1, 2 & 3 small molecule) and best standard of care (BSC) or placebo and BSC. Taking fruquintinib along with BSC had median OS of 9.30 months (95% CI 8.18-10.45) versus 6.57 months for participants receiving BSC and placebo (95% CI 5.88-8.11) (p-value < 0.001). The hazard ratio was 0.65 (95% CI: 0.51-0.83), meaning patients in the fruquintinib arm had 35% lower risk of dying. Moreover, median PFS was 3.71 months in the treatment arm (95% CI 3.65-4.63) and 1.84 months in the control group (95% CI 0.21-0.34) (p-value <0.001). The hazard ratio was 0.26 (95% CI 0.21-

0.34). Fruquintinib demonstrated a positive narrow side effect profile consisting of clinically manageable on-target (VEGR 1, 2 & 3) side effects like hypertension. Additionally, poster presentations on three collaborator-led trials with savolitinib (c-Met inhibitor) continued to highlight its applicability in treating c-Met-driven cancers. Ongoing data from a Phase II trial of sulfatinib (VEGFR 1, 2 & 3, FGFR1, CSF-1R inhibitor) in advanced medullary thyroid cancer were presented as well. See our [update note](#), “ASCO data set up fruquintinib for China launch”.

MorphoSys: Data on MOR202 and MOR208 presented

MorphoSys presented data from clinical trials of MOR202 (anti-CD38 antibody) and MOR208 (anti-CD19 antibody) at ASCO and at its investor and analyst event.

- MOR202 (abstract [8024](#)): Updated data from an ongoing Phase I/IIa study in heavily pre-treated r/r MM patients in three arms: MOR202 (n=18), MOR202 in combination with lenalidomide (n=15) and MOR202 in combination with pomalidomide (n=11), in each case with low-dose dexamethasone. Median PFS was 4.7 months, not reached and 17.1 months, respectively. ORR was 29%, 86% and 55%, respectively. The most frequent adverse events of grade 3 or higher were neutropenia, lymphopenia, and leukopenia in 42%, 40%, and 33% of patients, respectively.
- MOR208 (L-MIND study, abstract [7514](#)): this study is a single-arm Phase II trial of MOR208 plus lenalidomide in patients with r/r DLBCL ineligible for transplantation, poor prognosis and a median 73 years of age. Data from 34 patients showed an ORR of 56% (CR 32%). Well tolerated, only 27% of patients required a reduction of lenalidomide. This compares better than historic data on lenalidomide as monotherapy and in combination with rituximab or obinutuzumab (ORR 28%-45%; CR 7%-22%). More mature data will be presented at the American Society of Haematology (ASH) meeting in December 2017.

Our coverage on MorphoSys can be found [here](#).

PharmaMar: endometrial cancer data takes centre stage

PharmaMar presented data from a mid-stage study in 97 patients with advanced endometrial cancer (abstract [5586](#)). Lurbinectedin (PM01183) was evaluated as monotherapy and in two doses in combination with doxorubicin and in combination with paclitaxel. The best ORR was seen in combination with doxorubicin, with 28% ORR in Cohort A (3-5 mg flat dose of lurbin. plus dox 50 mg/m² both at day 1) and 44% ORR in Cohort B (2 mg/m² of lurbin. plus dox 40 mg/m² both at day 1). DCR was 85% and 83% respectively. Median PFS was 7.8 months and 7.7 months respectively. On the back of these data the company plans to initiate a Phase III trial for US registration.

Additionally, PharmaMar presented data from Yondelis (trabectedin) and lurbinectedin in BRACA1 and BRACA2 positive breast cancer, Yondelis in mesothelioma and soft tissue sarcoma and Yondelis in AML and r/r myelodysplastic syndrome (MDS). A summary of these studies can be found [here](#). Our coverage on PharmaMar can be found [here](#).

Prima Biomed: Combination data on IMP321 and chemo

Prima Biomed presented interim data on the combination of IMP321 (an LAG3 fusion protein that is an MHC class II agonist) and paclitaxel in patients with metastatic breast carcinoma (mBC). The [poster](#) showed that paclitaxel plus 6mg or 30mg of IMP321 had an ORR of 47% (all PR) and disease control rate (DCR) of 87% in 15 patients treated. Note that the expected historical PR for paclitaxel alone is c 30%. Cytokine release syndrome was the only serious adverse event related to IMP321. Our coverage on Prima Biomed can be found [here](#).

Viralytics: Update on Cavatak plus Yervoy in PD-1 failures

Viralytics presented an update on the combination of Cavatak (oncolytic coxsackievirus) and ipilimumab (abstract [3014](#)). In 13 patients treated with the combination and who had previous PD-1 treatment, the best ORR was 23.1% (3/13), and DCR was 62%. A best ORR of 67% (8/12) was observed in advanced melanoma patients naïve to prior checkpoint therapy. Adding these two subsets, ORR for all patients was 44% (11/25). There was only one Grade 3 treatment-related adverse event: ipilimumab-related elevated liver enzymes. Although caution must be exercised when doing cross-trial comparisons, oncolytic virus T-Vec (Imlygic, Amgen) in combination with ipilimumab in patients who were 98% naïve to immune checkpoint therapy reported a best ORR of 38.8% (n=98) in data presented at the conference. We view these data as positive given the scarcity of studies on patients who have progressed after treatment with an immune checkpoint inhibitor and the need to better understand how these patients can be treated.

Our coverage on Viralytics can be found [here](#).

Key takeaways

- CAR-Ts are expected to become a commercial reality soon; with two products under FDA review, we expect potential approvals in or before Q417. Upside remains significant as products generate positive data in new targets and earlier lines of treatment along with improved manufacturing.
- According to Evaluate Pharma, there are no fewer than 765 IO combination trials that involve PD-1 or PD-L1. Most of these trials are early stage, uncontrolled, non-randomised and in a small number of patients.
- Additionally, there is a large heterogeneity in the patient population of these clinical trials, with many different tumour types, prior lines of treatment, etc, hence cross-trial comparisons are virtually impossible.
- In order to gain investors' confidence, companies should first demonstrate good single agent activity before combining their products with others.
- Targeted therapies are relevant and generating good data despite the immunotherapy focus.
- We look forward to next data readouts in order to have a clearer picture of the evolution of the immunotherapy landscape; in particular, the highly anticipated data from AstraZeneca's Mystic study of durvalumab (anti-PD-L1) and tremelimumab (anti-CTLA4) in first line NSCLC. The study is expected to readout in H217.

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