EP Vantage's 2016 Asco backgrounder

26 May, 2016

When researchers and investors gather in Chicago next week for what is often the sector's most newsworthy meeting, the cancer congress Asco, they will do so in the context of a fast-moving oncology world that has seen the attention shift to immunology and adoptive cell therapies. And while these cutting-edge techniques are likely to grab headlines at the conference, news of the more everyday mechanisms of small molecules and antibodies will also fill column inches.

A review of *EP Vantage's* cancer coverage from the past six months reveals that a number of tumour types, such as liver and pancreatic cancers, could see some critical data emerge this year. Meanwhile, data on mechanisms like Parp inhibition and CAR-T therapies are also keenly awaited, for clues as to their real potential.

The articles gathered here highlight recent breakthroughs and setbacks in a number of cancer areas over the past six months, and flag the approaching data points that remain keenly awaited.

None of these articles has been updated for events that happened post publishing. So for example in liver cancer Bayer's Stivarga met the primary endpoint in the phase III Resource trial – great news for an intractable tumour type.

In late-stage pancreatic cancer, however, the pipeline has been decimated in recent months, with several compounds crashing out. One casualty Threshold Pharmaceuticals will be presenting data from its phase III Maestro trial showing how the hypoxia-activated prodrug failed to improve overall survival compared with the chemotherapy drug gemcitabine.

And, despite the recent failure to demonstrate overall survival in the Eclipse trial with its cancer vaccine CRS-207, Aduro will be presenting an update on its ongoing Stellar pancreatic cancer trial. The study has one crucial difference – alongside combining CRS-207 with GVAX Pancreas it also incorporates Bristol-Myers Squibb's checkpoint inhibitor Opdivo.

In AML, Celator will present results at Asco from its successful pivotal study of Vyxeos, a study flagged in our February article about this field.

Many of the issues raised in our look at the cancer vaccine field will no doubt be discussed at the conference, with much incremental data due to be presented. However, this remains a controversial

area of research, and the science strongly suggests that stimulating the immune system with a vaccine as monotherapy will not work; this point was recently proved by Celldex and Newlink, as well as Aduro.

Meanwhile Parp inhibition will also be a focus for many, in the light of the failure of Lynparza in the Gold study in gastric cancer. However, our article on the ovarian space shows that crucial data are awaited from several Parp molecules in this cancer type – the fate of this mechanism of action is far from sealed.

And finally Juno, Kite and Novartis will report updates on their CAR-T candidates. While no one is expecting revelations or vastly new data from Juno and Kite the presentations should include increased patient numbers and longer follow-up data compared with previous presentations. Novartis, however, has one of the most hotly awaited CAR-T presentations of the Asco meeting with its data from a trial of eight CTL019-treated patients retreated with CTL119.

Jon Gardner and Robin Davison will be providing extensive coverage of the conference for *EP Vantage*. Follow them on twitter via @ByJonGardner, @RobinDavison2 or contact by email JonathanG@epvantage.com, RobinD@epvantage.com.

For the background on all of these issues, read our articles below:

Therapy areas:

Pharma class:

Therapy focus – New kidney cancer data emerges in time for Asco

Published May 24, 2016

Yesterday's positive topline result with Cabometyx in first-line renal cell carcinoma could hardly have come at a more opportune moment for Exelixis, arriving just days before Asco, the world's largest cancer conference. The result from the Cabosun phase II trial could tip the balance in its favour against Bristol-Myers Squibb's anti-PD1 juggernaut Opdivo, which was launched several months before Cabometyx in this indication (see table).

Physicians can now speculate over whether the still unknown but apparently statistically and clinically significant progression-free survival advantage over Sutent justifies Cabometyx's move into first-line use. Sutent has been the de facto first-line standard of care since 2006. Exelixis plans to disclose the Cabosun data at a future scientific meeting.

The announcement also gives Exelixis something with which to make a splash at Asco, having had the chance to reveal mature overall survival results from its pivotal Meteor study of Cabometyx thwarted. The FDA's earlier-than-expected approval meant that data emerged on the package insert last month.

Moment in the Cabosun

Whether Exelixis can allude to the Cabosun result at Asco or not, the conference should provide a forum for a lively debate on the relative merits of Cabometyx and Opdivo in the approved second-line indication.

Doctors will also be able to consider the role for the other new agent that has just entered the RCC field, namely Eisai's Lenvima, which won a rapid approval – based on a phase II study – for use in combination with Afinitor in second-line patients.

Thus there are now three new choices for second-line RCC: Opdivo and Cabometyx as monotherapies, and Lenvima/Afinitor in combination. A side-by-side comparison of the pivotal data suggests that Cabometyx offers a 4.9-month, Opdivo a 5.4-month and the Lenvima/Afinitor combo a 10.1-month OS benefit.

However, the cross-trial comparison is compromised by the fact that Opdivo recruited better-prognosis patients, as seen by the control arm performance, and that Eisai's data came from a smaller phase II study. The control arm is, however, the same in all three cases: Afinitor alone. Moreover, the relative improvement in survival, as shown by hazard ratio, was greatest for Cabometyx, albeit by a small margin over Lenvima/Afinitor.

Cross-trial data comparison: new second-line RCC therapies

Drug	Cabometyx	Opdivo	Lenvima/ Afinitor
PFS	7.4 vs 3.8mths (HR=0.58, p<0.0001)	4.6 vs 4.4mths (HR=0.88, p=0.1135)	14.6 vs 5.5mths (HR=0.37)
OS	21.4 vs 16.5mths, (HR=0.66, p=0.0003)	25.0 vs 19.6mths (HR =0.73, p=0.0018)	25.5 vs 15.4mths (HR=0.67)
ORR	21% vs 5% (p<0.0001)	25% vs 5% (odds ratio=6.05 p<0.001)	37% vs 6%

Source: Company press releases

Before the Cabosun trial outcome sellside analysts had assumed that doctors would probably mostly use an immune checkpoint inhibitor ahead of a tyrosine kinase inhibitor, which meant that most of Cabometyx's sales would come in what is effectively the new third-line setting, after Sutent and Opdivo. But this could now change if the Cabosun data demonstrate a significant advantage from its earlier use.

But Cometriq might not be the only drug moving up the therapy lines shortly. The outcome, due imminently, of the S-trac study could position Sutent in the adjuvant setting in patients at high risk of recurrence. This study could make the Pfizer drug suitable for immediate post-nephrectomy use.

If Cabosun does establish Cabometyx as the first-line agent of choice it could have some implications for several ongoing phase III studies that use Sutent as control. These include the three combination studies involving checkpoint inhibitors: Javelin-Renal-101 of avelumab plus Inlyta, CheckMate-214 of Opdivo and Yervoy, and Immotion151 of Tecentriq plus Avastin.

Phase II and III trials in RCC

Product(s)	Company	Study	Therapy line	Enrolment	Design	Trial ID	Data
Phase III							
Sutent	Pfizer	S-TRAC	Adjuvant	720	vs placebo	NCT00375674	Apr 2016
rocapuldencel-T	Argos	ADAPT	1L	450	Sutent+/-	NCT01582672	Apr 2017
Inlyta	Pfizer	ATLAS	Adjuvant	700	vs placebo	NCT01599754	Jun 2017
Tivozanib	AVEO	TIVO-3	>3L	322	vs Nexavar	NCT02627963	Mar 2018
Avelumab + Inlyta	Pfizer	Javelin Renal 101	1L	583	vs Sutent	NCT02684006	Jun 2018
Opdivo + Yervoy	Bristol-MyersSquibb	CheckMate214	1L	1,099	vs Sutent	NCT02231749	Jun 2019
Tecentriq + Avastin	Roche	Immotion151	1L	830	vs Sutent	NCT02420821	Jun 2020
Phase II (selected)							
TRC105	Tracon	-	2-3L	168	Inlyta+/-	NCT01806064	Jul 2016
CRLX101	Cerulean Pharma	-	3-4L	110	vs SoC	NCT02187302	Sep 2016
Tecentriq +/- Avastin	Roche	Immotion150	1L	305	vs Sutent	NCT01984242	2016
Vargatef	Boehringer Ingelheim	-	1L	99	vs Sutent	NCT01024920	Feb 2017
MLN0128 +/- MLN1117	Takeda	-	1L	189	vs Afinitor	NCT02724020	May 2017
Dalantercept	Acceleron	-	3L	174	Inlyta+/-	NCT01727336	Dec 2017
AGS-16C3F	Agensys	-	>3L	134		NCT02639182	Jan 2018

Source: EvaluatePharma® May 2016

While the introduction of new agents should represent welcome improvements in the treatment of RCC, it is clear that that there will have to be more scientific debate on the merits of these drugs.

Key RCC data from Cabometyx, Opdivo and Lenvima at Asco

Abstract	Detail	Date/time/location
4506	OS data from Meteor study of Cometriq	Oral abstract: Jun 5, 10:12-10:24am. Hall D2
4558	Sub-group of Meteor study with bone metastases	Poster board: #180 Jun 6, 1:00-4:30pm. Hall A
4547	Outcomes based on prior VEGFR TKI and PD-1 therapy in Meteor study	Poster board: #179 Jun 6, 1:00-4:30pm. Hall A
4552	Correlation of response with OS from Checkmate 025 study of Opdivo	Poster board: #174 Jun 6, 1:00-4:30pm. Hall A
4507	Long-term OS in previously treated patients with advanced RCC from 010/003 Opdivo phase I and II studies	Oral abstract: Jun 5, 10:24-10:36am. Hall D2
4508 4509	Analyses of treatment beyond disease progression from CheckMate-025 study	Poster boards: #131 and 132, Jun 6, 1:00-4:30pm. Hall A. Discussed at 4:45-6:00pm, Arie Crown Theater
4553	Subgroup analyses and updated overall survival from the phase II trial of Lenvima	Poster board: #175. Jun 6, 1:00-4.30pm. Hall A

Source: http://abstract.asco.org

Author: Robin Davison

Ovarian cancer field readies for phase III readouts

Published March 18, 2016

Ovarian cancer specialists are in for a lively few months, with a run of pivotal trial readouts, two or more filings and the outcome of an EU submission for a long-forgotten project – events that could collectively move the field forward.

Any such development will be welcome as ovarian cancer remains a difficult-to-treat disease that has seen little progress in recent years (see table). Moreover, it has so far not been much of a target for immuno-oncology, which has taken great strides in other indications.

Some progress was made with the late 2014 conditional approval of a targeted agent, AstraZeneca's Lynparza, but the mainstay of treatment remains surgery followed by platinum and taxane chemotherapy. Nevertheless, a review of the field reveals a full phase III pipeline, with 11 different agents being examined in a total of 15 studies, and a further six agents in or entering registration-directed phase II or II/III trials.

Moving towards approval

Four of the phase III agents are Parp inhibitors, namely Lynparza, Tesaro's niraparib, Clovis's rucaparib and AbbVie's veliparib. The first three are being studied as maintenance therapies in BRCA-mutant patients, an approach thought to take best advantage of Parp inhibition's role in DNA repair. AbbVie, though, is conducting a larger study of veliparib in combination with first-line chemo, enrolling both wild-type and BRCA-mutant patients.

AstraZeneca's Solo-2 trial should read out this quarter, but some analysts believe that data are more likely later in the year. If this is the case, Tesaro's Nova trial will probably be the first of the Parp studies to report. This evaluates three different subpopulations based on patients' mutation status, and effectively has three opportunities to achieve a positive result (*Therapy Focus – Parp inhibitor class set to come of age in 2016, March 1, 2016*).

Tesaro also expects data from its Quadra phase II trial in fourth-line ovarian cancer around the same time as Nova reports, and believes the combined data sets would support an NDA submission planned for the second half.

Lynparza somewhat controversially gained early US approval – despite a negative advisory committee vote – for third/fourth-line use based on a subgroup analysis of gBRCA mutant patients. This highlighted the fact that regulators, perhaps mindful of the relative lack of new agents in ovarian cancer, were keen to give physicians new therapies.

Back from the dead

One surprise is that AstraZeneca's almost forgotten anti-VEGF tyrosine kinase inhibitor cediranib – which was pretty much consigned to history with a phase III failure in colorectal cancer in 2012 – is in fact under EMA review for ovarian cancer. The project was quietly filed in July 2015 based on phase II data and thus must now be approaching a decision.

AstraZeneca is seeking approval as a monotherapy in Europe, although cediranib is being developed in combination with Lynparza in the third-line setting in an NCI-sponsored phase II/III study, Cocos.

In the shorter term, AstraZeneca could face competition to Lynparza in 2017 from Clovis, which is expected to start a rolling NDA for its Parp inhibitor rucaparib in the second quarter. This will be for platinum-sensitive, relapsed, BRCA-mutant disease, based on the phase II Ariel-2 study in the fourth-line setting.

Clovis is also conducting Ariel-3 in third-line treatment, which is expected to complete enrolment in the next few months and render results around a year later.

Phase III trials in ovarian cancer

Project	Company	Study	Therapy line/subtype	Enrolment	Design	Trial ID	Data
Lynparza	AstraZeneca	Solo-2	>2L maintenance, gBRCA mutant	297	vs placebo	NCT01874353	Feb 2016
Niraparib	Tesaro	Nova	3L maintenance, pt-sensitive, gBRCA mutant	490	vs placebo	NCT01847274	Q2 2016
Perjeta	Roche	-	<3L Recurrent Pt-resistant, Low HER3 mRNA expression	208	vs chemo	NCT01684878	Apr 2016
Lynparza	AstraZeneca	Solo-1	1L maintenance, gBRCA mutant	397	vs placebo	NCT01844986	Jul 2016
Rucaparib	Clovis	Ariel-3	>3L maintenance, pt-sensitive	540	vs placebo	NCT01968213	Q2 2017
binimetinib	Array	Milo	2-4L, low grade serous	360	vs physician's choice	NCT01849874	H2 2017
Lynparza	AstraZeneca	Solo-3	3L relapsed gBRCA mut	411	vs single agent chemo	NCT02282020	Dec 2017
Vigil Ovarian (gemogenovatucel-T)	Gradalis	Vital	1L maintenance	574	vs placebo	NCT02346747	Dec 2017
Niraparib	Tesaro	Prima	1L maintenance, pt-sensitive, HRD-positive	305	vs placebo	NCT02655016	Mar 2018
Avelumab	Pfizer	Javelin Ovarian 200	<3L, pt-resistant/refractory	550	PLD +/-	NCT02580058	Mar 2018
Yondelis	J&J/Pharmamar	-	3L, BRCA mutant	670	PLD +/-	NCT01846611	Sep 2018
Lurbinectedin	Pharmamar	Corail	<4L, pt resistant	420	vs PLD/topotecan	NCT02421588	Oct 2018
Veliparib	Abbvie	-	1L maintenance	1100	carbo-tax +/-	NCT02470585	Jan 2019
Lynparza	AstraZeneca	-	>3L maintenance, pt-sensitive, -relapsed, sBRCA or HRR mutant	167	vs placebo	NCT02392676	Jun 2019
Yondelis	Pharmamar/J&J	Innovatyon	<3L, partial pt sensitive	588	vs carboplatin (+PLD)	NCT01379989	Dec 2019

Source: EvaluatePharma® March 2016

Regulators have been prepared to accept PFS as a primary endpoint in ovarian cancer, and indeed most of the pivotal phase III studies use this. An exception is Pfizer/Merck KGaA's Javelin Ovarian 200 study of the PD-L1 inhibitor avelumab. This is one of only two immuno-oncology approaches in the disease, the other being Gradalis's personalised cancer vaccine Vigil.

Ovarian is the fifth-most common cancer affecting women and has a 46% five-year survival rate. Other than achieving earlier diagnosis, there has been relatively little improvement in chemo in recent years, so it will be welcome indeed if some positive data emerge in 2016.

Author: Robin Davison

Hopes rise for a breakthrough in leukaemia logjam

Published February 25, 2016

2016 might finally see some tangible progress in acute myeloid leukaemia, a notoriously difficult indication where the "7+3" chemotherapy regimen of cytarabine and daunorubicin has held sway for 40 years as the frontline standard of care.

That progress will almost certainly come in the form of Novartis's midostaurin, which has shown a survival advantage in combination with standard of care in the subset of AML patients harbouring FLT-3 mutations. However, improvements could also come from Celator Pharmaceuticals, which is poised to report results from its pivotal study with Vyxeos, a liposomal reformulation of 7+3 (see table).

Breaking through

In December, Novartis reported results from the phase III Ratify trial of midostaurin, showing a 23% improvement in overall survival. The project subsequently gained breakthrough therapy designation, and given Novartis's plan to file in the first half it could see approval towards the end of this year.

Meanwhile, Celator last week confirmed that its phase III trial, named 301, had reached the number of events required to trigger an overall survival analysis, and that results would become available before the end of March.

Unusually, the 301 study has already rendered a positive result for a key secondary endpoint, induction response rate, where last year Celator reported a 14-point improvement, with 47.7% of patients on Vyxeos achieving a complete response with or without platelet recovery, versus 33.3% for conventional 7+3 *(Celator could quietly break leukaemia record, June 25, 2015).* The US microcap obviously hopes that this will translate into a survival advantage.

Celator's study enrolled patients aged 60 to 75 with secondary AML – those whose disease arose as a result of myelodysplastic syndromes or was related to prior therapy for another cancer type. This is a subgroup with few treatment options.

This choice of setting was driven partly by ethical constraints as Celator could not treat younger, de novo AML patients – who can tolerate 7+3 – when it was not known whether its therapy was superior. Nevertheless, if the 301 study establishes Vyxeos as superior to 7+3 in secondary AML, physicians would likely extrapolate its use to *de novo* patients in preference to the conventional regimen.

Volasertib and sapacitabine

Two other phase III AML studies are due to report this year, both in the front-line setting in older patients. These are the Polo-AML-2 trial of Boehringer Ingelheim's volasertib, and the now almost forgotten Seamless study of Cyclacel's sapacitabine.

Cyclacel's failed an interim analysis for futility last year, but unusually the DSMB still recommended its continuation to a conclusion. Hopes are therefore very low, but Seamless might possibly suggest that equivalence or non-inferiority, and Cyclacel might claim a benefit thanks to its less IV infusion-heavy dosing schedule. However, it would still have to go before the regulators on bended knee.

One company that is already doing this is Sunesis, which has filed vosaroxin in europe in relapsed/refractory AML, despite its Valor study missing its primary endpoint in 2014. The filing is for the sub-population of patients over 60 years old, and Sunesis thinks the EMA is willing to be generous in its interpretation of the rules, given the lack of alternatives.

There is some precedent for this, with the EMA's approval of Dacogen for elderly patients with AML in 2012. The FDA, however, declined to consider this approach last year.

As well as Novartis's midostaurin, in the past month a second agent, AbbVie and Roche's venetoclax, received breakthrough therapy designation – in combination with hypomethylating agents as front-line therapy for elderly patients with AML, where it is in phase I.

Phase III studies in AML

Project	Company	Study	Therapy line	Enrolment	Design	Trial ID	Data
Vyxeos	Celator	301	Older, 1L sAML	309	vs 7+3	NCT01696084	Mar 2016
Volasertib	Boehringer Ingelheim	Polo-AML-2	Older, 1L AML	666	+/-cytarabine	NCT01721876	Jun 2016
Sapacitabine	Cyclacel	Seamless	Older, 1L AML	485	+/-decitabine	NCT01303796	N/D (est 2016)
Quizartinib	Daiichi Sankyo	–	R/R, FLT3-ITD+	326	vs salvage chemo	NCT02039726	May 2017
Guadecitabine	Otsuka	–	Older, 1L AML	800	vs TC	NCT02348489	Dec 2017
Idasanutlin	Roche	–	R/R AML	440	+/-cytarabine	NCT02545283	Apr 2018
Iomab-B	Actinium	Sierra	R/R, allo-HSCT	150	vs conventional care	NCT02665065	Apr 2018
Oral Vidaza	Celgene	Quazar AML-001	Maintenance for pts in CR	460	+/- BSC	NCT01757535	Aug 2018
Treosulfan	Medac	–	Allo-HCST	960	vs busulfanRIC	NCT00822393	Jan 2019
CC-90007/AG-221	Celgene/Agios	Idhentify	Older, R/R,IDH2+	280	vs convention therapy	NCT02577406	Apr 2019
Quizartinib	Daiichi Sankyo	Quantum-First	1L, FLT3+ AML	536	+/- induction SoC	NCT02668653	Jan 2020
Gilteritinib/ASP2215	Astellas	–	R/R AML,FLT3+	369	vs salvage chemo	NCT02421939	Mar 2020
Pracinostat	MEI Pharma	–	1L, elderly	N/D	+/-azacitidine	N/D	N/D
Vadastuximab talirine	Seattle Genetics	–	1L, elderly	N/D	+/- HMA	N/D	N/D

Source: EvaluatePharma® February 2016

Eight other agents are in phase III for AML, according to an analysis by *EP Vantage*. This group is expected to be joined by MEI Pharma's pracinostat and Seattle Genetics' vadastuximab talirine later this year.

MEI plans to study its HDAC inhibitor in combination with Vidaza in elderly, front-line AML, pitching it in the same space as volasertib and Otsuka's decitabine follow-up, guadecitabine. Meanwhile, Seattle plans a study to investigate its ADC in combination with hypomethylating agents in older AML patients.

Given that AML has been a pharmaceutical development graveyard for so long, it would be heartening to see some of the pivotal readouts and some progress in the field.

Author: Robin Davison

Hopes rise for a liver cancer breakthrough in 2016

Published February 19, 2016

2016 offers the hope of becoming a breakthrough year for advanced hepatocellular carcinoma, with no fewer than six phase III trials involving five novel targeted agents likely to render results, an unprecedented number.

However, all of these agents are going up against a condition that has been notoriously intractable to pharmaceutical development (see table). Despite ranking among the most common forms of malignant disease, HCC has the fewest therapeutic options of any major cancer, with Bayer's Nexavar the sole approved drug in the indication.

EP Vantage's analysis of the field shows there are 11 agents currently in or entering phase III studies, and around a futher 15 in phase II. Among the more promising mid-stage candidates are Lilly's galunisertib, Merck KGaA's tepotinib and Astellas/Medivation's Xtandi.

Of the six agents expected to have 2016 phase III readouts, only two are risking going up against Nexavar, which itself has only shown a relatively modest 2.8-month increase in overall survival versus placebo. Those are Eisai's Lenvima, for which data are due in April, and Bristol-Myers Squibb's Opdivo. All the others are being tested in the second-line setting.

Common tactic

Seeking approval for second-line HCC has become a common tactic, owing to the lack of options after progression on or intolerance to Nexavar. This also gives the added benefit of allowing placebo to be used as control.

Taking this approach is the little-known US company Polaris, which should have first data readout this year with ADI-PEG20, a pegylated arginine deaminase. Polaris hopes that ADI-PEG20 will starve the tumour of arginine, an amino acid crucial to tumour cell metabolism and growth, by depleting it from the blood. The only data available are from a single-arm phase II study that showed a median OS in a mixed first/second-line population of 7.3 months. The company told *EP Vantage* that results of the phase III study of ADI-PEG 20 would be released at Asco.

Results are also due imminently from Bayer's Resource study of Stivarga. Bayer's choice of the second-line setting is surprising because Stivarga is so closely related chemically to Nexavar, so it is not immediately clear why it should show an additional benefit in Nexavar failures.

Exelixis will be hoping to gain a second additional indication for its tyrosine kinase inhibitor Cometriq based on the Celestial study, after that drug's recent trial success in renal cell carcinoma.

ArQule and its partners Kyowa Hakko Kirin and Daiichi Sankyo are conducting two phase III studies of tivantinib, a Met inhibitor, both of which should render results this year. These enrol only patients with high Met status, who represent about 50% of all HCC patients. Overexpression of this receptor is related to higher recurrence rates after surgery, while high c-Met expression correlates with shorter survival.

The Metiv-HCC study will shortly undergo an interim analysis, with a possible early efficacy stop, and will reach the required number of events for its final analysis by the end of the year.

Lilly is the only other company to have pursued patient selection in HCC, testing Cyramza in patients with elevated alpha-fetoprotein in the Reach-2 study. This approach was developed after an analysis of its earlier Reach study, which showed a non-significant benefit in the overall population.

Phase III trials in advanced hepatocellular carcinoma

Project	Company	Study	Therapy line	Enrolment	Design	Trial ID	Data
ADI-PEG20	Polaris	-	2L	636	vs placebo	NCT01287585	Due
Stivarga	Bayer	Resource	2L	560	vs placebo	NCT01774344	Feb 2016
Lenvima	Eisai	-	1L	954	vs Nexavar	NCT01761266	Apr 2016
Cometriq	Exelixis	Celestial	2L	760	vs placebo	NCT01908426	Oct 2016
Cyramza	Lilly	Reach-2	2L, elevated alpha fetoprotein	399	vs placebo	NCT02435433	Oct 2017
tivantinib	Daiichi Sankyo/Arqule	Metiv-HCC	2L, high cMet	368	vs placebo	NCT01755767	Dec 2016
tivantinib	KHK	Jet-HCC	2L	160	vs placebo	NCT02029157	Dec 2016
apatinib	Jiangsu HengRui	-	2L	360	vs placebo	NCT02329860	Jan 2017
Opdivo	BMS	CheckMate 459	2L	726	vs Nexavar	NCT02576509	May 2017
Livatag	Onxeo	Relive	2L	390	vs BSC	NCT01655693	Jul 2017
Pexa-Vec	Sillagen	Phocus	1L	600	Nexavar +/-	NCT02562755	Oct 2017
donafenib	Suzhou Zelgen	-	1L	600	vs Nexavar	NCT02645981	Dec 2018

Source: EvaluatePharma® February 2016

Multiple failures

All of these companies should know that HCC will be a tough nut to crack. In the past decade the disease has seen multiple phase III trial failures, including many with agents that have approvals in other cancer indications. Pfizer's large phase III trial of Sutent, for example, failed even to demonstrate non-inferiority to Nexavar.

AbbVie's linifanib, which was also tested against Nexavar, and Roche's Tarceva, which was given in combination with the Bayer drug, also failed. Meanwhile, Bristol-Myers-Squibb's brivanib was examined unsuccessfully in first and second-line settings, and Novartis had no better luck with Afinitor in second-line HCC.

NCCN guidelines do recommend several chemotherapy regimens for post-Nexavar use, including gemcitabine/oxaliplatin, capecitabine alone or in combination with oxaliplatin, doxorubicin or gemcitabine/cisplatin. All of these have shown some marginal benefit based on small phase II trials.

Although HCC remains one of the most difficult cancers, it is surprising that Nexavar has been the standard of care for almost a decade. It would be a huge development if one or more of the 2016 readouts changed this.

Author: Robin Davison

Pancreatic cancer 2016: this time it's (getting) personal

Published February 5, 2016

The pancreatic cancer pipeline lost Threshold Pharmaceuticals' evofosfamide and OncoMed Pharmaceuticals' tarextumab in recent weeks, but 2016 should nevertheless be an important year for the indication with four phase III trials due to read out, with careful patient selection a growing theme.

Ten pivotal phase III studies with eight agents are under way in this notoriously intractable cancer. Those due to render results this year include the Pillar and Impress studies of NewLink Genetics' cancer vaccine, algenpantucel-L, and the Pancrit-1 study of Immunomedics' radiolabelled MUC-1 antibody yttrium Y-90 clivatuzumab tetraxetan (see table).

However, the first trial to report data will be the Janus-1 study of Incyte's Jakafi, pencilled in for April. This is the first of two pancreatic cancer studies with the Jak 1/2 inhibitor, the other being Janus-2, which is due to report mid-2017.

Modest expectations

Expectations for both of these trials are modest at best, especially given the recent termination of a phase II study in metastatic colorectal cancer for lack of efficacy *(Incyte falls victim to the biotech bear market, January 28, 2016).*

Both Janus studies selectively enrol patients with high levels of C-reactive protein (CRP), a biomarker of inflammation, as this was the subgroup in which Jakafi showed efficacy in the earlier phase II Recap trial in pancreatic cancer. This had tested Jakafi second line and showed patients with high CRP to have a 53% reduction in risk of death, with a p value of 0.01.

This makes the studies some of the first in pancreatic cancer to attempt to select patients based on a biomarker. The highly heterogeneous nature of the disease might be responsible for the failure of most chemotherapeutics so far, and identifying subgroups with biological characteristics amenable to targeted therapies could eventually mirror lung and breast cancers.

Biomarkers

AstraZeneca's phase III study of Lynparza is also testing a patient-selection approach. The trial enrols patients with gBRCA mutations whose disease has not progressed on first-line platinum chemo. Evidence from breast and ovarian cancers suggests that BRCA-mutant cancers are highly sensitive to Parp inhibitors and platinum-based agents. Lynparza is already approved for ovarian cancer.

The Lynparza study is not due to report until 2017. Other agents with 2017 pivotal readouts are Eleison Pharmaceuticals' glufosfamide, Orient Pharma's NC-6004, a novel micellar formulation of cisplatin, and Gilead's Jak inhibitor momelotinib.

AB Science appears to be conducting a study to validate an undisclosed biomarker that it retrospectively identified in a failed phase III trial with mastitinib, though few details have been revealed – hence this is excluded from this analysis.

Phase III trials in pancreatic cancer

Project	Company	Study	Therapy line	Enrolment	Design	Trial ID	Data
algenpantucel-L	NewLink Genetics	Impress	resected, adjuvant	722	gem (+5FU/radiation) +/-	NCT01072981	Jun 2016
algenpantucel-L	NewLink Genetics	Pillar	borderline resectable	302	FOLFOX/FOLFIRINOX +/-	NCT01836432	Dec 2016
Glufosfamide	Eleison Pharmaceuticals	-	2L	480	vs 5FU	NCT01954992	May 2017
Nanoplatin	Orient Europharma/ Nanocarrier	-	1L	290	gemcitabine +/-	NCT02043288	Jun 2017
Lynparza (olaparib)	AstraZeneca	-	1L main, gBRCA mut	145	vs placebo	NCT02184195	Oct 2017
Momelotinib	Gilead Sciences	-	1L	430	gem/Abraxane +/-	NCT02101021	Dec 2017
PEGPH20	Halozyme	Halo-301	1L , HA-High	420	gem/Abraxane +/-	NCT02715804	Oct 2018
Abraxane	Gilead Sciences	Apact	adjuvant	800	gemcitabine +/-	NCT01964430	Apr 2019

Source: EvaluatePharma® February 2016

If any of the 2016-17 pivotal studies are successful, evolving standards might still make it difficult to draw conclusions from across-trial comparisons, particularly in the second-line setting, where there is no consensus.

This could change, of course, if Merrimack's Onivyde becomes the new standard after the Napoli-1 study established a benefit for Onivyde against 5FU/leucovorin alone – though physicians can only speculate how much benefit the new liposomal irinotecan conferred over the native molecule, which is used in a currently-used combination, Folfiri.

Recent analysis of Napoli-1 looked at CA19-9, and established that the benefit correlates with baseline CA19-9 levels, something that might become a useful biomarker.

EP Vantage has identified a number of registration phase II programmes, all in the first-line setting, two of which are due to render results this year: Halozyme's PEGPH20 and Momenta's necuparanib. Halozyme is notable for also using a biomarker approach, and it also plans a phase III study in high-HA patients later this year.

Given that pancreatic cancer has historically proven to be so intractable it would be easy to dismiss hopes for positive results in the upcoming pivotal readouts. However, there is a sufficiently large number over the coming year to give grounds for some cautious optimism.

Author: Robin Davison

Asco preview – Two directions for novel small-molecule classes

Published May 19, 2016

Release of abstracts ahead of the Asco cancer meeting shows one novel drug class looking very promising and the other stumbling badly.

CDK 4/6 inhibitors from Lilly, Novartis and Pfizer have confirmed their place in breast cancer, and now encouraging data in ovarian cancer have emerged. Parp inhibitors from AbbVie and Clovis Oncology, meanwhile, have failed to extend this drug class beyond its current comfort zone of ovarian disease.

Going up

Data from Lilly's CDK 4/6 abemaciclib might have been some of the most eagerly awaited of this year's major cancer congress, and did not disappoint. The project runs the risk of being third to market behind Pfizer's Ibrance and Novartis's ribociclib, but better tolerability and single-agent activity could help it compete.

Eight-month data from the single-arm Monarch 1 trial in late-stage metastatic HR-positive, Her-negative breast cancer showed that the agent as a monotherapy produced confirmed objective responses, comprising complete and partial responses, in 17.4% of 132 patients. Median progression-free survival was 5.7 months.

Leerink analyst Seamus Fernandez wrote that he would not raise his sales forecast for abemaciclib because of "advancing competition and a less differentiated profile than we'd hoped" in the Monarch 1 interim findings – *EvaluatePharma's* consensus of sellside analysts forecasts $1.8bn in 2022.

His concerns about competition were heightened by Novartis's announcement yesterday that ribociclib's Monaleesa-2 study in first-line use had been stopped early because of efficacy *(Novartis first to make pre-Asco splash, May 19, 2016).*

Meanwhile, Ibrance has generated another strong set of data, with the Paloma-2 trial supporting findings from the open-label Paloma-1 study that earned accelerated approval. In combination with letrozole, Ibrance generated a 10-month progression-free survival benefit of 24.8 months, compared with 14.5 months for letrozole alone.

The 10-month benefit was similar to the Paloma-1 findings, although the progression-free survival in that trial was 20.2 months for Ibrance plus letrozole and 10.2 months for letrozole alone.

"This outcome implies a much larger market than we currently model and likely cements Ibrance's assumed leadership position," Mr Fernandez wrote.

Parps down

After its disappointing exit from the lung cancer space, Clovis Oncology has turned to the Parp inhibitor rucaparib as its next shot on goal. Data released in pancreatic cancer in the Asco abstracts do not provide much hope – enrolment in the trial was stopped because of minimal response in the first 15 patients.

Coming as this does the day after the one marketed Parp inhibitor, Lynparza, flopped in gastric cancer, it might not have come as much of a surprise *(Lynparza puts a small dent in Parp inhibitor optimism, May 19, 2016).*

AbbVie's veliparib, meanwhile, had a bad day in small-cell lung cancer. Its phase II trial in combination with temozolomide showed no significant benefit over chemotherapy alone in second and third-line patients – the share of patients alive and progression free at four months was 36% in the veliparib arm and 27% in the control arm.

Finally, Medivation's talazoparib, the value of which will be essential to any talks around a takeout by Sanofi, also had its troubles. A dosing trial using it in combination with carboplatin in patients with solid tumours revealed that haematological toxicities required dose reductions or delays in nearly all of the 24 enrolees; researchers suggested less frequent carboplatin dosing.

The progress of immuno-oncology has dominated much of the news at recent cancer meetings. Meanwhile, the biopharma sector is still making progress with small molecules, and the upcoming Asco meeting looks to have substantial data on these targeted agents.

Project	Study	Trial ID
abemaciclib	Monarch 1	NCT02102490
Ibrance	Paloma 2	NCT01740427
rucaparib	Rucapanc	NCT02042378
veliparib	n/a	NCT01638546
talazoparib	n/a	NCT02358200

Source: EvaluatePharma® May 2016

Author: Jonathan Gardner

Testing times for cancer vaccines

Published May 12, 2016

The catastrophic failure of NewLink Genetics' Impress phase III trial with HyperAcute pancreas earlier this week – in which the control arm appeared to outperform the study drug – was of such magnitude that observers have been left wondering what implications it has for the wider cancer vaccine field (see table).

Cancer vaccines have lamentably failed to make progress in recent years, in marked contrast with the great strides made with immune checkpoint inhibitors and the excitement over the potential offered by CAR-T therapies and engineered T-cell receptor approaches.

The Impress result was also the second major setback in the cancer vaccine field this year, the first being Celldex's failure with Rintega in glioblastoma. And looking back over the past couple of years, cancer immunotherapy has been marked by a succession of failed phase III trials, from Immatics' IMA901 in renal cell carcinoma to GlaxoSmithKline 's Mage-A3 and Merck KGaA /Oncothyreon's Stimuvax, both in non-small cell lung cancer.

Conventional wisdom is of course that cancer vaccines, like checkpoint inhibitors, have to be given early in the course of the disease to give the immune system time to keep the cancer in check. NewLink 's Impress trial tested exactly this hypothesis.

Not Impressive

The study tested HyperAcute pancreas, also known as algenpantucel-L, against placebo as adjuvant therapy in surgically resected pancreatic cancer patients.This is a small proportion of patients in whom the tumour is identified sufficiently early to undergo the radical Whipple procedure, which offers long-term benefits and might be curative.

Thus it is perhaps doubly disappointing that the Impress study drug showed a numerically and possibly even statistically inferior median overall survival (*NewLink's pancreatic cancer candidate fails to Impress, May 10, 2016).*

Fortunately for NewLink, its future has for some time rested on its promising immuno-oncology assets. The relative health of the cancer vaccines field is more dependent on the outcome of its two other HyperAcute studies.These are a second pivotal trial of HyperAcute pancreas in borderline resectable patients and a smaller phase II/III study of HyperAcute lung. Both are due to report at the end of this year, but after the result in Impress expectations are vanishingly low.

Indeed, with the notable exception of the Impact study of Provenge, all of the pivotal studies ever conducted with cancer vaccines to date have failed to demonstrate efficacy, despite often promising phase II studies.

And Provenge, burdened by high manufacturing costs and complex logistic issues, was of course a commercial failure, bringing down its debt-burdened originator Dendreon. Provenge now languishes within the troubled speciality pharma giant Valeant.

But there is still much activity in the cancer vaccine field. A review by *EP Vantage* suggests that there are at least 12 commercial cancer vaccines in phase III development, most of which are *ex vivo* modified autologous cell-based therapies like Provenge, and thus have the most complicated manufacturing economics.

Commercial cancer vaccines in phase III

Product	Company	Study	Indication and therapy line	Enrolment	Trial ID	Data
Prostvac	Bavarian Nordic /BMS	Prospect	mCRPC	1,298	NCT01322490	Aug 2016
HyperAcute pancreas/ algenpantucel-L	NewLink Genetics	Pillar	Pancreatic, borderline resectable	722	NCT01836432	Dec 2016
HyperAcute lung/ tergenpumatucel-L	NewLink Genetics	-	NSCLC, 2L	240	NCT01774578	Dec 2016
rocapuldencel-T	Argos Therapeutics	Adapt	RCC, 1L	450	NCT01582672	Apr 2017
DCCVAC	Sotio	Viable	mCRPC	1,170	NCT02111577	Dec 2017
Vigil/ gemogenovatucel-T	Gradalis	Gradalis	Ovarian, 1L maintenance	Vital	NCT02346747	Dec 2017
OSE2101	OSE Pharma	-	2-3L, NSCLC	500	NCT02654587	Mar 2018
NeuVax/ nelipepimut-S	Galena	Present	Early stage node-positive breast cancer	700	NCT01479244	Apr 2018
TT10: EB-VST	Tessa Therapeutics	-	Nasopharyngeal carcinoma	330	NCT02578641	Dec 2018
ICT-107	ImmunoCellular Therapeutics	-	Glioblastoma multiforme	414	NCT02546102	Dec 2019
OncoVAX	Vaccinogen	-	Adjuvant CRC	550	NCT02448173	Jul 2020
DCVax-L	Northwest Biotherapeutics	-	Glioblastoma multiforme	348	NCT00045968	N/A

Source: EvaluatePharma® May 2016

Bavarian carries the torch

Hopes of the cancer vaccine field are now carried by Bavarian Nordic's Prostvac, which could also be the next programme to report results. Bavarian 's Prospect study has already undergone one interim futility analysis this year, and has two more interim analyses to go, this time with the potential for early efficacy stops. Results may come this year or possibly early in 2017.

Next up is likely to be Argos Therapeutics, which could be one of three programmes to render results in 2017, possibly earlier if stopped early for efficacy at its second interim analysis, due sometime this year.

With optimism in short supply, it is surprising that there is still corporate activity going on in the space. Nevertheless, Australia's Prima BioMed earlier today announced a deal to transfer its CVac programme – which had been in a phase III study for ovarian cancer until that trial was stopped – to an effectively new US company, Sydys.

This represents a brave move for those investors backing Sydys, considering the challenges in the field. It may be a little too soon to write the obituary for cancer vaccines, but if there is any future here it must surely come from studies conducted in combination with checkpoint inhibitors.

There have been few such studies to date and none has reached or even got close to phase III. Perhaps expecting cancer vaccines to demonstrate efficacy as monotherapy first is simply too high a hurdle.

Author: Robin Davison

TG could benefit from Zydelig setback

Published March 29, 2016

Gilead ’s recent decision to terminate a number of clinical trials with Zydelig as a front-line therapy for chronic lymphocytic leukaemia because of serious adverse events raises the question of whether any of its competitors in the PI3K inhibitor space could receive a boost.

And, assuming that the Zydelig safety issues are not a class effect, the answer is that TG Therapeutics might do (see table). TG’s PI3K inhibitor TGR-1202 is in a phase III study for CLL and squarely targets the malignancy where both of the abandoned Gilead phase III studies were pitched.

However, TG's benefit could be short-lived due to the recent approval of J&J/AbbVie’s BTK inhibitor Imbruvica in front-line CLL.

Zydelig suspension

Earlier this month, Gilead disclosed that six Zydelig trials – including two of four ongoing phase IIIs – had been stopped after serious adverse events including deaths had emerged. Both of the now closed phase III studies were in previously untreated CLL, one in which the drug was added to bendamustine /Rituxan, and another in which it was being tested against chlorambucil, on top of Roche's Gazyva.

Four phase II studies have also been closed, and an investigator-sponsored trial in Waldenström's macroglobulinaemia is listed as suspended pending a safety review.

Ongoing phase III with PI3K inhibitors in haematological conditions

Project	Company	Study	Indication	Design	Trial ID
Zydelig	Gilead	Bridalveil	Previously treated iNHL	Rituxan + bendamustine +/-	NCT01732926
Zydelig	Gilead	Yosemite	Previously treated iNHL	Rituxan +/-	NCT01732913
Copanlisib	Bayer	Chronos -2	Rituxan - refractory iNHL	vs Placebo	NCT02369016
Copanlisib	Bayer	Chronos -3	>2nd-line, relapsed iNHL	Rituxan +/-	NCT02367040
Copanlisib	Bayer	Chronos -4	>2nd-line, relapsed iNHL	vs Placebo	NCT02626455
Duvelisib	AbbVie /Infinity	Duo	Relapsed or refractory CLL/SLL	Arzerra	NCT02004522
Duvelisib	AbbVie /Infinity	Dynamo + R	Previously treated FL	Rituxan +/-	NCT02204982
Duvelisib	AbbVie /Infinity	Bravura	Previously treated iNHL	Rituxan + bendamustine +/-	NCT02576275
TGR1202 + ublituximab	TG Therapeutics	Unity-CLL	Tx-naive or experienced CLL	vs Gazyva + chlorambucil	NCT02612311

Source: EvaluatePharma® March 2016

The closure of these studies leaves Zydelig in two ongoing phase III studies: Bridalveil and Yosemite, which are both in previously treated indolent non-Hodgkin lymphoma (iNHL).

At last year's Ash meeting Gilead reported solid evidence of Zydelig's efficacy in previously treated CLL. The "115" phase III study showed a 67% reduction in the risk of disease progression or death, and a 45% reduction in the risk of death, at an interim analysis. At the time the group said it planned to file a supplemental NDA this year.

Zydelig is approved for relapsed CLL in combination with Rituxan, and for relapsed follicular and small lymphocytic lymphoma in patients who have received at least two prior systemic therapies. However, it was already looking sickly before even the latest events; it carries a black box for various serious adverse events, and this warning meant that it had been losing out to J&J/AbbVie's BTK inhibitor Imbruvica, which has a much cleaner side-effect profile.

Game over?

The approval earlier this month of Imbruvica for front-line CLL, based on the Resonate-2 study, could seal the fate of PI3K inhibitors in this indication. Data published at Asco last year showed that Imbruvica reduced risk of death or disease progression by 84% compared with chlorambucil, and the overall response rate of 86% was also significantly greater than chlorambucil's 35%.

EvaluatePharma data suggest consensus 2020 sale expectations for Zydelig of around $950m, a figure that although stable for some time fell by around 30% in mid-2014, when competition from Imbrivica first materialised. The number should now fall further.

Whether or not TG's TGR-1202 gains an advantage in front-line CLL at the expense of Zydelig, Gilead's drug faces potential competition in NHL from the two other PI3K inhibitors that are in development for haematological indications, AbbVie/Infinity's duvelisib and Bayer's copanlisib, *EP Vantage's* review of the space suggests.

AbbVie and Infinity expect to report topline data from the Dynamo phase II study of duvelisib in refractory iNHL and to complete an interim analysis of the Duo study in relapsed/refractory CLL in the third quarter of 2016.

At one point Gilead had looked like it could build a therapy franchise in haematological cancer around Zydelig, but this strategy is no longer tenable.This must put more pressure on Gilead to make a bold acquisition to shore up its presence in oncology.

Author: Robin Davison

Parp inhibitor class set to come of age in 2016

Published March 1, 2016

The Parp inhibitor class has made a remarkable comeback from the nadir it reached when Sanofi's iniparib failed in separate phase III trials for triple-negative breast and non-small cell lung cancers. That recovery was catalysed largely by a single event: the late 2014 conditional approval of AstraZeneca 's Lynparza, a project that had itself been discontinued but was later resurrected with a post-hoc analysis of phase II data.

Thus, despite the class having been almost written off by many, Parp inhibitors have recovered strongly with five agents now in a total of 18 phase III studies. Moreover, six of these phase III trials are due to render results this year, an analysis by *EP Vantage* shows (see table).

Going Solo-2

AstraZeneca is likely to be the first to report data with progression-free survival results from its Solo-2 study of Lynparza due imminently. This study is designed to show a benefit as maintenance therapy in third-line, relapsed BRCA mutant ovarian cancer.

This is close to the drug's current indication, which is for the treatment of germline BRCA (gBRCA) mutant ovarian cancer patients in the salvage setting – fourth line or later – where a 34% response rate had been seen in a 137-patient study and led to an accelerated approval.

If positive, Solo-2 should support a move to full approval, although Lynparza 's label in ovarian cancer may also be expanded on the basis of the Solo-1 study in first-line gBRCA disease, which renders results a few months later.

Two phase III studies with Lynparza in other cancer indications, namely the Gold study in second-line gastric cancer and the Olympiad study in adjuvant treatment of gBRCA mutant breast cancer, are also expected to read out in the first half of this year.

Another study that renders results in the April to June timeframe is Tesaro's Nova phase III trial of niraparib in third-line ovarian cancer. This has a complex design that recruited two cohorts based on gBRCA mutant status. The gBRCA mutants will be evaluated first, and results will no doubt compared to Lynparza 's in Solo-2.

The study also examines a subgroup of gBRCA wild types with homologous recombination deficiency (HRD) and then a third group of all non-gBRCA mutants in a hierarchical fashion. This effectively gives Nova three opportunities to render a positive result.

Tesaro expects data from its Quadra phase II trial in fourth-line ovarian cancer around the same time, and with Nova , this is expected to support an NDA submission in the second half. Tesaro is also conducting phase III trials in gBRCA mutant breast cancer, called Bravo, and first-line maintenance ovarian cancer, called Prima .

Breast cancer

A phase III study with AbbVie 's veliparib in neo-adjuvant early stage triple negative breast cancer – which does not select on the basis of BRCA mutation status –and the Embraca trial with Medivation's talazoparib in metastatic breast cancer, are also due to report results this year. AbbVie has four other phase III studies underway with veliparib, studiously avoiding ovarian cancer and pursuing other solid tumours.

Clovis is potentially further down the regulatory track than its one phase III study with rucaparib suggests, as it holds breakthrough therapy designation for tumour BRCA -mutated ovarian cancer in patients who had had two prior platinum-containing regimens. Pending results from the phase II Ariel -2 trial, Clovis plans to submit an NDA for the treatment of fourth-line or later ovarian cancer with either BRCA mutations or the "BRCAness" signature.

The breakthrough therapy designation was based on Study 10 and data from part 1 of Ariel-2. Study 10 included 17 patients with relapsed, platinum-sensitive gBRCA ovarian cancer, and showed a response in 12/17 (71%). The Ariel-2 data showed a response in 15/23 (65%) of ovarian cancer patients with BRCA mutations.

Phase III studies with Parp inhibitors

Project/ Company	Study	Indication/ Therapy line	Enrolment	Design	Trial ID	Data
Lynparza /AstraZeneca						
	Solo-2	BRCA mut ovarian, >2L	297	placebo	NCT01874353	Feb 2016
	Gold	2L gastric cancer	500	paclitaxel +/-	NCT01924533	Apr 2016
	Olympiad	gBRCA1/2 mut mBC	310	physicians choice	NCT02000622	May 2016
	Solo-1	BRCA mut ovarian, 1L	397	placebo	NCT01844986	Jul 2016
	Polo	gBRCA mut pancreatic cancer, 1L maintenance	145	placebo	NCT02184195	Oct 2017

	Solo-3	Relapsed gBRCA mut ovarian cancer, 3L	411	Single agent chemotherapy	NCT02282020	Dec 2017
	-	Pt-sensitive, relapsed ovarian cancer, sBRCA or HRR mutant, maintenance Tx	167	placebo	NCT02392676	Jun 2019
	OlympiA	mBC , gBRCA1/2 mutations	1500	placebo	NCT02032823	Mar 2020
Niraparib /Tesaro						
	Nova	Maintenance Tx, 3L pt-sensitive, gBRCA mut ovarian cancer	490	placebo	NCT01847274	Q2 2016
	Bravo	HER2 negative, gBRCA mut breast cancer	306	physician's choice	NCT01905592	Sep 2017
	Prima	Maintenance Tx, HRD-positive ovarian cancer, response to front-line Pt chemo	305	placebo	NCT02655016	Mar 2018
Veliparib /Abbvie						
	-	neoadjuvant, early stage TNBC	624	carboplatin +/- veliparib vs chemo	NCT02032277	Apr 2016
	-	HER2-negative, BRCA -associated breast cancer	270	carbotax +/-	NCT02163694	Jan 2017
	-	Tx-naïve, squamous NSCLC	975	carbotax +/-	NCT02106546	Apr 2017
	-	1L, non-squamous NSCLC, current or former smokers	525	carbotax + veliparib vs physicians choice	NCT02264990	Nov 2017
	-	Continuation maintenance Tx, ovarian cancer	1100	carbotax +/-	NCT02470585	Jan 2019
Talazoparib /Medivation						
	Embraca	mBC with gBRCA mutation	429	vs physician's choice	NCT01945775	Jun 2016
Rucaparib /Clovis						
	Ariel -3	Switch maintenance Tx, Pt-sensitive ovarian cancer	540	placebo	NCT01968213	Q2 2017

Source: EvaluatePharma® March 2016

Parp (poly ADP-ribose polymerase) inhibitors are designed to disable the tumour cell's ability to repair damaged DNA, leading to synthetic lethality, without affecting normal cells. In most cases, the strategy has been to exploit the fact that BRCA1 /2-mutated cells have DNA repair mechanisms that are already impaired.

EvaluatePharma consensus data suggest the sell-side believes 2020 sales of niraparib will be $660m, followed by around $600m for Lynparza and velirapib and $220m for rucaparib, respectively. However, it's a fair bet that these figures are not additive. BRCA mutation prevalence in most cancers is very low, suggesting there may only be a small commercial opportunity for Parp inhibitors unless studies show effectiveness in non-BRCA populations.This may take some time yet.

Author: Robin Davison

How do you solve a problem like CAR-T relapse?

Published December 22, 2015

Several companies' CAR-T therapies have already produced impressive remission rates in leukaemia patients, but a high rate of relapses continues to cloud their long-term potential, especially considering the likely cost.

Several strategies have emerged to overcome this, one of which is Novartis 's design of a CAR construct with a humanised antigen-binding region, the theory being that the commonly used murine CARs are being rejected by the immune system. But if this is the way forward it could leave Novartis's CTL019 – the industry's most-advanced CAR-T asset – and other murine constructs in a bind.

There is little data to go on at present, but one of the most hotly awaited presentations of the recent Ash meeting concerned the first data from a trial of six CTL019 -treated patients retreated with Novartis 's new humanised, CD19 -targeting CAR, CTL119 . Three of these went into complete remission, one of which was still ongoing at almost six months.

Dr Shannon Maude, of the Children's Hospital of Philadelphia, said it was particularly impressive that one of the remitting patients had had no response to the murine CTL019. It is early days, but further positive data in a larger patient set would put Novartis in a quandary: should the group even bother filing CTL019, or should it just switch to CTL119?

This might hit sentiment behind Novartis and the entire CAR-T space alike, given that the Swiss firm is the furthest advanced here, and it still hopes to submit CTL019 for approval next year. Switching to CTL119 would naturally imply a later filing.

Little is known about other players' plans to develop humanised CARs; Kite has made a patent filing for one, while Juno refers to a bonus due to its R&D head, Mark Frohlich, on first patient dosing in a pivotal trial with a fully humanized CAR-T cell product.

CD19 -positive or antigen escape?

Of course such considerations relate to so-called CD19 -positive relapses – where patients' leukaemia continues to express the CD19 antigen, with relapse due to waning CAR-T cells or loss of the CAR construct.

In the latest cut of Novartis's CTL019 data a highly impressive 93% of ALL patients went into complete remission after a month, though less impressively this rate was down to 30% by one year. At Ash the

Children's Hospital of Philadelphia's Dr Stephan Grupp said CD19 -positive relapse was responsible for a third of recurrences *(Ash– CAR-T struggles to travel beyond leukaemia, December 8, 2015).*

The remaining two thirds relapse because of loss of the CD19 antigen, and clearly require an entirely different retreatment approach. One strategy is to target a separate antigen, and fortunately in B-cell malignancies an alternative one seems to exist: CD22.

The leading project here is JCAR018, an anti-CD22 CAR derived from work at the NIH that Juno bought from Opus Bio last year for about $120m. A first-in-human trial of JCAR018 featured at a separate Ash poster detailing a cohort of seven evaluable ALL patients, six of whom had been treated with an anti-CD19 CAR, and five of whom had had CD19 -negative relapse.

Complete remission was seen in two patients. It is early days here, too, and the best that can be said beyond initial efficacy hints is that there was no severe cytokine release syndrome, suggesting relative safety of JCAR018 , though most of the patients were given the lowest CAR-T cell dose.

Anti-CD22 projects in development

Mechanism	Project	Company	Status (indication)
Anti-CD22 MAb-calicheamicin conjugate	Inotuzumab ozogamicin	Pfizer /UCB	Phase III (ALL & NHL)
Anti-CD22 MAb-PE38 conjugate	Moxetumomab pasudotox	AstraZeneca	Phase III (HCL)
Anti-CD19 & CD22 MAb	OXS-1550 /DT2219ARL	Oxis / University of Minnesota	Phase II (NHL)
Anti-CD22 MAb-monomethyl auristatin E conjugate	Pinatuzumab vedotin	Roche / Seattle Genetics	Phase II (NHL)
Anti-CD22 MAb-yttrium 90 conjugate	IMMU-102 (Y-90 epratuzumab tetraxetan)	Immunomedics	Phase II (NHL)
Anti-CD22 CAR-T therapy	JCAR018 / LG740	Juno / Opus Bio	Phase I
Anti-CD22 CAR-T therapy	UCART22	Cellectis	Research (ALL)
DT-CD22 fusion protein	CD22-DIDT	Angelica Therapeutics	Research
Anti-CD19 & CD22 CAR-T therapy	CD19 /CD22 bispecific CAR	NCI (NIH)	Research

Source: EvaluatePharma® December 2015

Selection of antigens against which CAR-T therapies are being developed has tended to follow development of antibodies, and CD22 is no exception, but it is interesting that anti-CD22 MAbs, including MEDI-553 and IMTOX 22-97, have all failed in oncology, while UCB 's epratuzumab failed in lupus.

Several antibody-drug conjugates are in development, as well as UCART22 , an allogeneic CAR-T therapy from Cellectis that also has a dCK gene knockout to confer fludarabine resistance.

At Ash the NCI's Dr Daniel Lee said he was continuing to enrol CD19 -escaped patients into a CD22 CAR-T study, though all the data and IP arising from this will presumably belong not to the NCI's CRADA partner Kite, but rather to Juno.

Dr Lee also cited a planned study of a bivalent CD19 -CD22 CAR, a highly unusual single CAR construct that was featured at an Ash poster. The NCI authors concluded that the order of the CD19 and CD22 binding domains, and the length of the linker, affected function, and despite some evidence of activity further optimisation is needed before this enters the clinic.

Persistence problems

When it comes to CD19 -positive relapses, developers of CAR-T therapies have to contend with a separate problem, namely the lack of persistence of the CAR construct on the T cells, or its inability to generate a sufficiently sustained response.

Since there are differences in the design of different players' CAR constructs it is hoped that further data will shed light on which of these differences might affect persistence. For instance, Kite employs a gamma-retrovirus to transfect its construct, which uses a CD28 co-stimulatory domain, while Novartis 's uses lentiviral transfection and a 4-1BB co-stimulatory element.

Juno has both: JCAR015, a CD28 /gamma-retroviral construct from Memorial Sloan Kettering (MSK), and JCAR017, a 4-1BB /lentiviral one from the Fred Hutchinson Cancer Research Center. Again there is a lack of hard evidence, but Dr Grupp of the Philadelphia children's hospital says his construct, which is used by Novartis , enables persistence of around four years, versus around 30 days for the MSK /Kite projects.

During a recent investor call Dr Grupp stated that CD28 co-stimulation tends to give a strong early response but the T cells then "burn out", while gamma-retroviruses are known to risk causing gene silencing.

"Solely based on the data that's published right now, I'd say there's more compelling data that CD28 versus 4-1BB is a bigger part of the [persistence] equation than lentiviral versus gamma-retroviral," he speculated. "But that is just a guess."

If further trials do substantiate this view then Kite especially will be left with some rethinking to do.

Project	Company	Study	Trial ID	Ash abstract
CTL119	Novartis	CTL019 ALL study treating some relapsing pts	NCT02228096	683
JCAR018	Juno	Multi-dose, 57 pts with B-cell malignancies	NCT02315612	1324
CD19 /CD22 bispecific CAR	NCI (NIH)	Early work on design of CAR construct	–	4427

Source: https://ash.confex.com/ash/2015/webprogram/

Author: Jacob Plieth

Editorial team

Lisa Urquhart
Editor
LisaU@epvantage.com
@LisaEPVantage

Madeleine Armstrong
Reporter
MadeleineA@epvantage.com
@medtechma

Amy Brown
News Editor
AmyB@epvantage.com
@AmyEPVantage

Joanne Fagg
Content Manager
JoanneF@epvantage.com
@JoEPVantage

Jonathan Gardner
Deputy News Editor
JonathanG@epvantage.com
@ByJonGardner

Edwin Elmhirst
Editorial Assistant
EdwinE@epvantage.com
@EPVantage

Jacob Plieth
Senior Reporter
JacobP@epvantage.com
@JacobPlieth

Robin Davidson
Contributor
RobinD@epvantage.com
@RobinDavison2

Elizabeth Cairns
Medtech Reporter
ElizabethC@epvantage.com
@LizEPVantage

Evaluate – Headquarters – Evaluate Ltd, 11-29 Fashion Street, London E1 6PX United Kingdom
Tel: +44 (0)20 7377 0800 – Fax: +44 (0)20 7539 1801

Evaluate – North America – EvaluatePharma USA, Inc., 15 Broad Street, Suite 401, Boston, MA 02109 USA
Tel: 1-617 573-9450 – Fax: 1-617 573-9542

Evaluate – Japan – Evaluate Japan KK, Akasaka Garden City 4F, 4-15-1 Akasaka, Minato-ku, Tokyo 107-0052, Japan
Tel: +81 (0) 80 1164 4754

www.evaluategroup.com