NOT FOR THE FAINT OF CAR-T

The CAR-T therapy landscape in 2015

January 2015
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NOT FOR THE FAINT OF CAR-T

To say that recent progress in CAR-T therapies was greeted with market enthusiasm last year could be the understatement of 2014. And as 2015 gets under way this area looks set to be one of the top investment themes of the year.

There are two opposing ideas: on the one hand the two biggest biotech names, Juno Therapeutics and Kite Pharma, now face massive risks to their valuations in a crowded space that will likely be characterised by extensive litigation.

This is not to say that their projects are in the lead group for no reason, of course, or that their market caps are about to collapse. But they are not for the faint of heart, especially considering that any slip, for instance in terms of a new safety signal, could hammer their share prices. Moreover, Kite has yet even to negotiate an exclusive licence to its CAR-T project from academia; deal frenzy has pushed these asset prices sky high, so Kite’s licence is unlikely to come cheaply.

Against this, however, is the reality that deals will continue to get done, and continued desperation to get on the bandwagon for all things CAR-T-related will drive activity. Numerous stocks could end up basking in reflected glory.

With the key risks come opportunities, especially for the smaller stocks. For example, Bellicum Pharmaceuticals offers a straightforward bet on the US FDA demanding a CAR-T safety switch to allay toxicity concerns; Cellectis’s focus on allogeneic CAR-Ts plays straight into concerns that the cost of autologous therapy will prove unsustainable in the real world.

Smart investors, of course, need to appreciate the numerous red flags that many following this space are now ignoring. An understanding of the risks should point to the trends that will shape this sector in the coming year as the various players fight it out for tiny advantages and the market looks to identify the next hot trend in T-cell therapeutics.
If you followed last year’s explosion of enthusiasm in CAR therapies you might have assumed that this was a super-novel approach that had just burst onto the scientific stage. In fact work on the synthetic modification of a patient’s T cells to make them target a specific disease has been ongoing for over 20 years.

But it is only relatively recently that two things happened: the CD19 antigen was pinpointed as an ideal target in haematological cancers thanks to its almost exclusive presence on B cells and B-cell precursors; and the current, so-called second-generation CAR (chimaeric antigen receptor) was designed.

This marked the transformation of CARs from just another interesting scientific concept to one of today’s most promising oncology therapies. Progress has accelerated since the 2013 American Society of Hematology (ASH) meeting, and right now CAR therapy is already being hailed by some as a revolution that – in some patients – amounts to a cure.

While the science behind the current CAR constructs might be complex, the idea is actually relatively simple. In broad outline, the approach harnesses a patient’s own immune system to direct it specifically against a disease.

A CAR is a synthetic receptor designed to target a specific tumour cell surface antigen, and the approach involves genetically modifying T cells (usually the patient’s own) to make them express such a receptor on their surface.

The resulting CAR-T cells recognise the tumour antigen in question, and on binding with it the CAR sends an intracellular signal to the T cell, prompting the destruction of the cancer cell.

UNTEMPERED ENTHUSIASM

A scientific advance of such magnitude has, naturally, been accompanied by untempered enthusiasm from investors desperate to jump into “the next big thing”.

Look no further than the fund-raising record of Kite Pharma, Juno Therapeutics and Bellicum Pharmaceuticals – three Nasdaq-listed US companies that offer pure-play exposure to cell therapy. All have seen huge demand for their offerings to the extent that every investor approach has yielded more cash than initially targeted.

**Investors have flocked to CAR-T stocks**

<table>
<thead>
<tr>
<th>Company</th>
<th>Market cap ($bn)</th>
<th>Private</th>
<th>IPO</th>
<th>Post-IPO</th>
<th>IPO Premium to range</th>
<th>% rise on 1st days trading</th>
<th>Share price since float</th>
</tr>
</thead>
<tbody>
<tr>
<td>Juno Therapeutics</td>
<td>5.1</td>
<td>310</td>
<td>304</td>
<td>0</td>
<td>45%</td>
<td>46%</td>
<td>116%</td>
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<tr>
<td>Kite Pharma</td>
<td>3.6</td>
<td>35</td>
<td>147</td>
<td>216</td>
<td>31%</td>
<td>71%</td>
<td>415%</td>
</tr>
<tr>
<td>Bellicum</td>
<td>0.8</td>
<td>107</td>
<td>161</td>
<td>0</td>
<td>19%</td>
<td>26%</td>
<td>60%</td>
</tr>
</tbody>
</table>

Source: EP Vantage
A huge inflow of money into this space was triggered by the last edition of the ASH meeting, at which CAR therapies stole the show. Bellicum and Juno both floated on December 19, shortly after the meeting ended. Cellectis, a CAR-T company based in Paris and traded on the NYSE Alternext market, has announced plans for a secondary listing on Nasdaq.

Much potential lies in CAR therapy. However, with investors willing to value such early-stage technologies at such huge valuations, it is clear that important risks are being ignored. The market appears to be steadfastly refusing to heed the lessons of the biotech boom and bust of 1999/2000.

Nevertheless, none of this means that CAR companies do not offer smart investors plenty of opportunities to benefit, and indeed in the early days of 2015 this space looks like being one of the top investment themes of the year.

THE SCIENCE

T-cell manipulation has a long history, having initially involved the expression of very basic CAR constructs in an effort to treat HIV. The first CARs had a very simple design, with a 1991 scientific paper describing a simple CD4 extracellular domain and an intracellular CD8ζ (zeta) intracellular signalling region.

Things moved on, and nowadays the favoured structure of a so-called second-generation CAR includes a complex scFv domain whose heavy and light chains mimic those of an antibody, plus an intracellular CD3ζ signalling section as well as a co-stimulatory domain (see below). Third-generation CARs have two co-stimulatory domains to increase potency further, though work here is very early.

Second-generation CAR construct

When the CAR-engineered T cell engages the target cancer surface antigen it triggers further multiplication of the cells in the body, and activation of a cytotoxic (cell-killing) response. These T cells have an “auto-regulatory” capability, in that they multiply in the presence of the target antigen, but their number falls as the target declines.
In its most advanced – autologous – version the actual therapy is a complex procedure, involving the collection of a patient's white blood cells via leukapheresis, and while these are outside the body certain T cells are isolated and transfected, usually using a viral vector, with the genetic material to make them express the desired CAR on their surface.

After this ex vivo modification the cells are expanded until their number reaches the desired “dose”, whereupon they are infused back into the patient.

THE KEY PLAYERS

Given how fast the T-cell therapy field has advanced in the past year it is worth remembering that only a couple of hundred patients have been treated with current CAR therapies, and only a handful of commercial players have sponsored clinical trials.

Still, investors wanting to bet on pure-play CAR therapies cannot access what at present looks like the sector’s most promising asset: at each of the past ASH meetings it was neither Juno nor Kite that stole the show, but rather Novartis, through its partnership with the University of Pennsylvania on CTL019.

Novartis/Penn

Last month two of the university’s leading CAR researchers, Drs Carl June and Stephan Grupp, presented data from a 39-patient paediatric relapsed/refractory acute lymphocytic leukaemia (ALL) study in which CTL019 produced nothing less than a 92% complete remission rate. Six-month duration of response was 76%, and six-month event-free survival was 70%.

These data came from a 64-patient ALL cohort that included 41 paediatric cases; the two remaining patients were pending evaluation. In total 135 patients have been treated so far with the CD19 CAR that Novartis has licensed, in patients with ALL as well as chronic lymphocytic leukaemia (CLL), lymphoma and myeloma, across six separate phase I and phase II studies.

Novartis aims to file CTL019 for ALL in 2016, followed by a submission for diffuse large B-cell lymphoma (DLBCL) a year later.

Juno/Memorial Sloan Kettering

Juno’s most advanced CAR-T project, JCAR015, is not far off. This is partnered with the Memorial Sloan Kettering Cancer Center, and reported an 89% complete remission rate in 27 evaluable adult patients with relapsed/refractory ALL. After a median six months’ follow-up 12 patients remained disease-free, including seven with over a year of follow-up, and seven without a subsequent hematopoietic stem cell transplant.

ALL is Juno’s primary focus; the group says it plans to begin a phase II trial in relapsed/refractory ALL in mid-2015, and believes that positive data from this trial could lead to initial US regulatory approval as soon as 2017.
Kite/NCI

Meanwhile, Kite’s lead, KTE-C19, will initially target non-Hodgkin’s lymphomas (including DLBCL and mantle cell lymphoma). The company has so far relied on clinical data generated by the National Cancer Institute (NCI), with whose surgery branch it has a co-operative research and development agreement (CRADA).

The company itself recently filed an IND to begin its first in-house trial of KTE-C19 in DLBCL this year – presumably once it has managed to sign an exclusive licence to it with the NCI. This study will aim to recruit 112 patients, and three additional studies, in mantle cell lymphoma, CLL and ALL, are also planned in 2015 – though these indications are still at the pre-IND stage.

At ASH 2014 the NCI’s Dr Daniel Lee reported data from a study of KTE-C19 in 21 adults and children who were also relapsed/refractory. Overall, complete remission was seen in 67% (one patient had DLBCL), while in the 20 with ALL the rate was 70%, and 52% of all-comers were still alive after a median 10 months’ follow-up.

Earlier data from 24 evaluable patients had shown an 83% overall response rate, 42% of the total being complete remissions, including 100% overall response in four indolent NHL patients.

Selected CAR-T projects: differences and similarities

<table>
<thead>
<tr>
<th>Academic group</th>
<th>Company</th>
<th>Co-stimulatory domain</th>
<th>Vector delivery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uni of Pennsylvania</td>
<td>Novartis</td>
<td>4-1BB</td>
<td>Lentiviral</td>
</tr>
<tr>
<td>Memorial Sloan Kettering</td>
<td>Juno</td>
<td>CD28</td>
<td>Retroviral</td>
</tr>
<tr>
<td>Fred Hutchinson</td>
<td>Juno</td>
<td>4-1BB</td>
<td>Lentiviral</td>
</tr>
<tr>
<td>NCI (NIH)</td>
<td>Kite Pharma</td>
<td>CD28</td>
<td>Retroviral</td>
</tr>
<tr>
<td>Baylor</td>
<td>Bluebird/Celgene</td>
<td>CD28</td>
<td>Retroviral</td>
</tr>
<tr>
<td>MD Anderson</td>
<td>Ziopharm/Intrexon</td>
<td>CD28, now changing to 4-1BB</td>
<td>Transposon/transposase</td>
</tr>
<tr>
<td>Institut Pasteur</td>
<td>Cellectis/Pfizer</td>
<td>4-1BB</td>
<td>Lentiviral</td>
</tr>
<tr>
<td>Baylor</td>
<td>Bellicum</td>
<td>MyD88 and CD40 (dual co-stim domain)</td>
<td>Retroviral</td>
</tr>
<tr>
<td>Dartmouth College</td>
<td>Cardio3</td>
<td>None (has DAP-10 transmembrane section)</td>
<td>Retroviral</td>
</tr>
</tbody>
</table>

Source: EP Vantage

Because Novartis’s CAR work is not the subject of biotech fund-raising efforts relatively little public information is available about it. We do know, however, that CTL019 is the first of several CAR projects that the Swiss group has highlighted in investor presentations.
A clinical trial started recently of huCART19, a next-generation version of CTL019. Presumably this is humanised to try and overcome loss of CAR-T cells that some groups have reported due to a response against the murine nature of the scFv region.

Importantly, Juno also has a second key partnership – with the Fred Hutchinson Cancer Center, which has undertaken some clinical work. Juno’s initial focus here is on the CD19-directed CAR-T project JCAR017, whose structure differs from that used in JCAR015.

In phase I JCAR017 has demonstrated an 85% complete remission rate in 13 evaluable patients with paediatric relapsed/refractory ALL, and is an important asset since it has shown the longest cell persistence in patients of any of Juno’s CD19-directed CAR-Ts.

Some analysts see the potential of JCAR017 in NHL as Juno’s main valuation driver. The company plans to start a phase I/II trial of JCAR017 in relapsed/refractory NHL this year, with a potential to move to a registration study in 2016.

Juno also plans to begin phase I testing for at least three more CAR candidates this year, and wants to start the first clinical testing of a CD19-directed “armored” CAR in one or more B-cell malignancies (see page 13).

There are of course considerations beyond clinical data in determining how advanced the various players are. Back in 2013, for instance, Novartis acquired a manufacturing site for processing the CAR-T cells. This previously belonged to Dendreon, the cancer vaccine company that collapsed under its debts last year. Juno aims to have a commercial facility online by the end of 2015.

**IN EARLIER DEVELOPMENT**

Beyond these three players clinical data are scarce. A slightly different approach, which uses non-viral gene transfer via a transposon/transposase DNA plasmid-based system called Sleeping Beauty, rather than lentiviral or retroviral transfection, is in development at the MD Anderson Cancer Center.

At ASH 2014 the hospital’s Dr Partow Kebriaei presented data in various malignancies, either with or without transplant, and intriguingly using CAR-T cells derived either from the patient or the donor.

Dr Kebriaei highlighted Sleeping Beauty’s safety, in particular the lack of cytokine release syndrome, and possible cost advantages. However, the relative safety of this approach could be due to it simply being less efficacious, as well as the fact that in the post-transplant setting the tumour burden is low.

Indeed, Dr Kebriaei’s data were underwhelming, showing complete remission rates of 80%, 46% and 36% in three leukaemia/lymphoma studies in various settings. Remarkably, however, the technology was licensed by two US biotechs, Ziopharm and Intrexon, on 13 January for $115m in equity.
Bluebird/Celgene

One clinical CAR-T project that is still somewhat under the radar is in development at the Baylor College of Medicine; this is noteworthy because the IP has been licensed to Bluebird Bio and Celgene.

Bluebird is, however, working on its own CAR-T constructs, which are still in preclinical studies. In March 2013 Celgene struck a deal to opt into any resulting Bluebird projects once they completed phase I; Celgene also has a separate collaboration with Baylor College.

Baylor’s own phase I trials target various CD19-expressing haematological malignancies, but perhaps the most intriguing is a study that tests a standard second-generation CAR-T as well as a third-generation construct. The former uses the CD28 co-stimulatory domain, whereas the latter comprises a dual co-stimulatory region of CD28 and 4-1BB.

Bellicum/Baylor

Baylor is also one of the hospitals that form the basis of the T-cell therapies being developed by Bellicum, which floated on the same day as Juno last year. For now Bellicum’s most advanced projects are a donor T-cell cell therapy for treating graft-versus-host disease, and a dendritic cell cancer vaccine.

Its CAR-T assets are still in preclinical trials, and are not expected to enter the clinic until 2016. Bellicum is, however, the most advanced developer of the so-called “suicide switch” technology, which could become extremely relevant in avoiding serious side effects (see page 12).

Cellectis/Pfizer/Servier

Another early-stage player well worth looking out for is the French biotech Cellectis, which was recently issued a US patent covering its meganuclease-based Talen gene-editing technology. This lies at the core of its CAR-T approach, which – in contrast to the other players – is allogeneic, implying an off-the-shelf product rather than one that relies on engineering a patient’s own cells.

Last June Cellectis, which not long before had restructured away from plant sciences to focus chiefly on CAR-T, struck a deal with Pfizer worth $80m up front. Its most advanced project is UCART19, and one of the advantages of such an off-the-shelf therapy would be relatively low cost. Cellectis had signed a separate deal over UCART19, worth $10m up front, with Servier in February.

When at ASH 2014 EP Vantage spoke to Cellectis’s vice-president of CART development, Julianne Smith, she said UCART19 was a typical second-generation CAR-T that additionally involved Talen gene editing to remove TCR-alpha on a T cells’ surface to avoid graft-versus-host disease; the removal of TCR-alpha is the key to the allogeneic approach.

A key event for Cellectis will be the start of clinical trials with UCART19, against CD19-expressing haematological malignancies, this year, once manufacturing has been refined.
### Key industry CAR-T projects and targets

<table>
<thead>
<tr>
<th>Company</th>
<th>Project</th>
<th>Antigen targeted</th>
<th>Indication</th>
<th>Status</th>
</tr>
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<tbody>
<tr>
<td>Novartis</td>
<td>CTL019</td>
<td>CD19</td>
<td>ALL, CLL</td>
<td>Phase II</td>
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<td></td>
<td>huCART19</td>
<td>CD19</td>
<td>various</td>
<td>Pilot study</td>
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<tr>
<td></td>
<td>MesoCART</td>
<td>Mesothelin</td>
<td>mesothelioma, pancreatic</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>huEGFRVIII</td>
<td>EGFRVIII</td>
<td>glioma</td>
<td>Preclinical</td>
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<td>Juno Therapeutics</td>
<td>JCAR015</td>
<td>CD19</td>
<td>B-cell ALL, r/r ALL</td>
<td>Phase I</td>
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<td></td>
<td>JCAR017</td>
<td>CD19</td>
<td>paed r/rALL</td>
<td>Phase I/II</td>
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<td></td>
<td>CD22 CAR</td>
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<td>B-cell cancers</td>
<td>Phase I/II</td>
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<td>L1CAM CAR</td>
<td>L1CAM</td>
<td>neuroblastoma</td>
<td>Phase I</td>
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<td></td>
<td>MUC16 &amp; IL5</td>
<td>MUC16 &amp; IL6</td>
<td>ovarian</td>
<td>Preclinical</td>
</tr>
<tr>
<td></td>
<td>“armored” CAR</td>
<td>ROR-1</td>
<td>CLL, solid tumours</td>
<td>Preclinical</td>
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<tr>
<td>Kite Pharma</td>
<td>KTE-C19</td>
<td>CD19</td>
<td>DBCL</td>
<td>Phase I (NCI trial)</td>
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<td></td>
<td>EGFRVIII</td>
<td>EGFRVIII</td>
<td>glioblastoma</td>
<td>Phase I/II (NCI trial)</td>
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<tr>
<td>Bluebird/Celgene</td>
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<td>ALL, CLL</td>
<td>Phase I</td>
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<tr>
<td>Ziopham/Intrexon</td>
<td>Sleeping Beauty</td>
<td>CD19</td>
<td>various, adjuvant, pre and post-transplant</td>
<td>Phase I</td>
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<td>Cellectis</td>
<td>UCART19</td>
<td>CD19</td>
<td>ALL, CLL</td>
<td>Phase I starting 2015</td>
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<td>UCART123</td>
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<td>UCART5T4</td>
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<td>UCARTCS1</td>
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<tr>
<td>Cardio3</td>
<td>CM-CS1</td>
<td>MICA, MICB &amp; ULBP6</td>
<td>AML, MDS, multiple myeloma</td>
<td>Phase I starting 2015</td>
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<td>Bellicum Pharmaceuticals</td>
<td>BPX-401</td>
<td>CD19</td>
<td>various</td>
<td>Phase I/II starting 2016</td>
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<tr>
<td></td>
<td>BPX-601</td>
<td>PCSA</td>
<td>solid tumours</td>
<td>Phase I/II starting 2016</td>
</tr>
</tbody>
</table>

*Source: EP Vantage*
THE RED FLAGS

Given the astonishing response rates and long remissions seen in some people, as well as the surrounding hype, it is well worth doing a reality check of the risks, which at the current valuations of Juno and Kite could have a serious effect if they should come to pass.

Who owns what?

For a start, there is a great deal of uncertainty as to where the intellectual property behind CAR-Ts lies – stemming directly from the fact that this work has been ongoing for decades, with academics having shared much of it among themselves. Now that progress has at last been made, and commercialisation efforts advance apace, what is left behind is a minefield of ownership rights.

Juno, for instance, has already spent considerable energy, and millions of dollars, in litigation with the University of Pennsylvania over the ownership of a patent it had licensed from St Jude Children’s Research Hospital. Further lawsuits are inevitable, and as if to prove the point Kite recently appointed a senior executive vice-president of intellectual property law.

In Kite’s case there is even less clarity over IP since the company is still reliant on obtaining exclusive CAR-T licences from the NCI. At present Kite and the NCI are operating under a CRADA expiring in August 2017 under which Kite has the option to negotiate an exclusive licence – something it has not yet done.

It might be that it will take the setting up of a network of cross-licensing deals between the various academic groups and corporate entities before any of these CAR-T projects is able to reach the market.

How much?

What about the cost of CAR-T therapy? The expense of these treatments is at present perhaps the single biggest elephant in the room.

Already we know that millions have been spent on R&D of CAR-T projects in the limited numbers of subjects where they have been tested. And the per-patient cost of an autologous, tailored cell therapy is likely to run into hundreds of thousands of dollars – even before a potential stem cell transplant is factored in.

Whether CAR-T therapy simply delays the time until patients are transplanted, or whether it is a replacement for transplant, is a directly related consideration. Dr Lee, presenting the Kite data at ASH, called CAR-T a “bridge to transplant”, but in the Juno study only 10 patients proceeded to transplant, while with Novartis’s CTL019 the number was just three.

“I would love CAR-T to be a replacement for transplant,” said Dr Grupp in December. “This is my fondest hope, but we’re not there yet.”

While patient-specific cell therapies represent the cutting edge of research, their economic proposition might ultimately be limited. Long-term investors wanting to bet on this scenario could do worse than look at Cellectis and its allogeneic CAR-T.
Toxic assets

Another huge risk to today’s exuberance is the side effects of CAR-T therapy, which include neurotoxicity and cytokine release syndrome, also known as cytokine storm. These are likely the result of large-scale T-cell activation, and both have been shown to correlate with disease burden and response.

Juno has been most prominently affected: last year two patients died as a result of severe cytokine release syndrome in a Memorial Sloan Kettering study of JCAR015, leading the FDA to suspend the trial. This hold was lifted just two weeks later, and a lower dose of CAR-T cells is now being administered.

In the coming year safety will be one of the most closely watched aspects of CAR-T therapy – notwithstanding many doctors’ insistence that it is controllable with steroids and the anti-IL-6 receptor MAb Actemra. Over a year ago – before the FDA clinical halt – The University of Pennsylvania’s Dr Grupp called Actemra a “game-changing [drug] in controlling cytokine release.” It still might prove not game-changing enough.

A look at the suicide switch

If side effects are set to remain a serious concern, especially in the FDA’s mind, what other strategies are under way to control them?

The most promising one at present seems to be the “suicide switch” – a feature additionally built into some CAR-T cells enabling them all to be destroyed very quickly in the event of severe cytokine syndrome, hopefully stopping the undesired side effect. Of course this work is very early, but the pioneer here is Bellicum.

Bellicum calls its “suicide switch” CaspaCIDe because it is based on caspase activation. It involves inserting, via a viral vector, an additional gene into the target T-cell, causing it to express the human caspase 9 protein fused to a drug-binding domain; this intracellular protein can persist for a long time after administration of therapy, but is inert – until a specific small molecule, rimiducid, is administered.

Administration of rimiducid prompts the dimerisation of these caspase 9 proteins, and this process activates caspase signalling, initiating cellular destruction (apoptosis). Bellicum has licensed rights to rimiducid (AP1903) from Ariad Pharmaceuticals for $50m.
While CaspaCIDe has yet to be tested in humans as part of a CAR-T cell, it is incorporated into Bellicum’s lead graft-versus-host T-cell therapy, which is in phase I/II. The company’s preclinical CAR project, BPX-401, is to use this technology. BPX-601, another CAR therapy also triggered by rimiducid, uses a different mechanism (separate from the receptor) that acts as an “on” switch.

BPX-401 incorporates two proteins, MyD88 and CD40, in a dual co-stimulatory domain; Bellicum claims that these are more potent than CD28 and 4-1BB. BPX-601 has no co-stimulatory domains, being activated solely by rimiducid; the aim is for rimiducid infusions to continue until the desired outcome is achieved, while in the event of side effects CAR-T cell activity can be attenuated by reducing the rimiducid administration schedule.

It was recently revealed that Juno, too, was working on a suicide switch of its own – presumably a move triggered by the deaths in the Sloan Kettering study. This consists of inserting a gene into the T-cell that causes the expression of an inactive truncated EGF receptor, in addition to the CAR; the receptor can be activated by a commercially available antibody like Erbitux, initiating rapid killing of the T-cells. JCAR017 is to use this technology.

Kite has not disclosed that it is working on anything similar, and Dr Grupp has confirmed that his University of Pennsylvania group is not.

There is one view in the market that because of the risk of toxicity the US FDA will not approve any CAR-T that does not include a safety feature to control the proliferation and survival of the engineered T cells. Investors taking this view will clearly find Bellicum and Juno interesting.

Juno is also exploring two further CAR variants designed to improve safety: bispecific CARs and “armored” CARs. A bispecific CAR incorporates a second binding domain to amplify or inhibit signalling, a feature that could increase CAR T-cells’ ability to distinguish between cancer cells and normal cells.

For example, a CAR T-cell could be engineered such that it would be triggered in the presence of one target protein, but if a second protein (associated with non-cancer cells) is also present it would be inhibited. Alternatively, it could also be engineered to require two target proteins to be present for maximum activation.

“Armored” CARs deliver cytokines like IL-12 or stimulatory signals to modify the tumour microenvironment and minimise systemic side effects. An example of such a signalling protein signal is IL-12, which can stimulate T-cell activation and recruitment. Both bispecific and “armored” technologies are at an early stage.

Relapses

Another worrying aspect of CAR therapy is the rate of relapse among patients who initially respond strongly; while all the leading CAR therapies have shown long-lasting effects, with continued T-cell persistence in some patients, in others there has either been no effect or patients have relapsed.
At least academics are agreed that if a patient does not respond initially they are unlikely to respond on subsequent treatment. But the fact that in some patients disease recurs is worrying, both in that it makes strong complete remission rates (i.e., “cures”) seem less impressive, and because it hikes the already considerable cost – especially if the next stage is stem cell transplantation.

Then again, it is important to distinguish between two different types of relapse. One is caused by a loss of the CD19 protein on a patient’s target tumour cells, called “antigen escape”. The other, so-called CD19-positive relapses, take place when levels of CAR-T cells in a patient wane in the continued presence of the CD19 target protein.

In recent trials of the Novartis and Kite projects some CD19-negative (antigen escaped) relapsing patients were enrolled into separate treatment with a CD22 CAR-T; CD22 is another B-cell-specific antigen. However, the CD22 CAR-T now appears to be in the hands of Juno, through an alliance this group has struck with the NCI and a private company called Opus Bio.

This instance of the same academic technology being used across multiple commercial projects underlines again the vagueness of the ownership status of CAR-T intellectual property. Wherever the IP lies, there is an ever-present threat of litigation hanging over all the players here (see above).

**Big pharma reluctance**

Highly transformative though the field of CAR T-cell therapy is, there are several other red flags that investors appear to be ignoring. While an acquisition premium is one factor driving valuations, it is notable that big pharma has so far taken very cautious steps into this space. Only Novartis seems to have fully embraced CAR-T, and presumably thanks to being an early entrant and licensing technology directly from academia its financial outlay has so far been relatively limited. Pfizer has done the deal with Cellectis, though this too was an early-stage alliance, and involved an up-front fee of just $80m.

Back in November Johnson & Johnson jumped into the space in a cautious way, striking a three-year discovery deal with Transposagen Biopharmaceuticals, a private US biotech. This will use Transposagen’s genome editing technologies to create the allogeneic CAR-T and CAR-natural killer cell projects.

Beyond this big pharma appears for historical reasons either to be focusing on other oncology approaches, or might still view CAR-T as too expensive to risk right now. Merck & Co, Bristol-Myers Squibb and Roche are making a push into checkpoint inhibition, for instance, while AstraZeneca has also made a bet on RNA therapy; GlaxoSmithKline has an alliance with Adaptimmune, a T-cell receptor company, but has put oncology on a back burner.
Financial flags

Juno has had to agree to significant future earnouts under its own technology licences with Fred Hutchinson and Memorial Sloan Kettering and, however unrealistic the triggering share price thresholds are, their presence indicates how much potential there is for Juno’s exuberant investors to be diluted.

As a side note, several key players in Juno’s management team are former executives of Dendreon; investors must presumably hope that these have learned from previous mistakes.

In terms of investment, Juno spent $44.5m in 2013 to acquire CAR-T technology from its academic collaborators, for instance. Unusually large future earnouts are also due – $375m to Fred Hutchinson and $150m to Memorial Sloan Kettering – triggered at up to $160 per share. The company also seems to be pre-empting shareholder litigation, employing a restrictive “fee-shifting” bylaw to deter dissident investors. At $5bn of market cap it seems that many of these warning signs are being ignored.

It is clear that the red flags for CAR-T therapy are numerous, from generating long-term efficacy and justifying pricing to the almost inevitable legal wrangling. However, perhaps the biggest threat hanging over this whole space – and one that will be very closely watched by investors – is safety.

It is unthinkable that there will not be any further adverse effect problems, and at current valuations the potential for these to wreak havoc with share prices cannot be overstated.

NEW TARGETS FOR OLD

With so much risk it is clear that stocks like Juno and Kite are now not for the faint of heart. But there are still a number of smaller players providing numerous investment themes. One of these is the search for future targets, which will hot up once significant inroads have been made into targeting haematological cancers and the low-hanging fruit of the CD19 antigen. Solid tumours, for instance, are still largely untested ground for CAR therapy.

Beyond CD22 future targets of interest for Juno include L1CAM (CD171), an antigen it plans to pursue with a CAR therapy in neuroblastoma, and ROR1, a protein overexpressed on NSCLC, triple-negative breast, pancreatic, prostate and several B-cell cancers. EGFRVIII has been listed as a glioblastoma target by Kite and Novartis, and the latter’s group has also run a phase I trial with a CAR against mesothelin for pancreatic cancer and mesothelioma.

Cellectis has a CD123 project in preclinical development, and recently signed an exclusive licence with Ohio State University to develop a CAR technology against the CS1 antigen for treating multiple myeloma. Bellicum has done early work on a CAR against PSCA-overexpressing solid cancers, and the NCI is recruiting into a trial of a VEGFR2-directed CAR therapy.

Celdara Medical, a private group, was developing a CAR-T cell construct using NKG2D, an activating receptor normally present on natural killer cells and targeting certain haematological and solid tumour antigens including MICA, MICB and ULBP6.
DEAL BANDWAGON

This brings up a second, related, theme: licensing deals and company and asset acquisitions to develop new targets or access new technologies.

The Celdara CAR-T business was recently bought by the Belgian group Cardio3 BioSciences for just $10m, and a phase I study for which Celdara had obtained an IND should begin shortly. This business also comprises an early-stage allogeneic CAR-T – like Cellectis’s this is also based on inactivation of the TCR-alpha gene, though using a different process.

Many companies no doubt see the CAR-T bandwagon as an opportunity too good to miss, and deal-making is sure to provide continuing share price catalysts. However, one obvious question is why, with the market valuing Juno and Kite in the billions of dollars, Celdara would have let a CAR project go for just $10m.

More indicative of the hype is the $115m in equity that Ziopharm and Intrexon handed across to access MD Anderson’s Sleeping Beauty CAR-T project. This shows the prices that even less than stellar CAR-T projects can fetch – a salutary lesson to followers of Kite, which has yet to secure an exclusive licence with the NCI to what is one of the most promising assets in the entire space.

It will also be interesting to watch whether big pharma makes a bolder entry into this field, and if it does then most of the smaller players’ share prices should benefit. It has to be said, however, that if big pharma really wanted an asset like Sleeping Beauty it would likely have made a move for it by now.

Still, a blueprint for positive share movement is the reaction seen in Juno and Bellicum stock when Amgen signed a target discovery alliance with Kite. It mattered little that Amgen’s move was still cautious, or that the tie-up had nothing to do with Kite’s lead CAR-T asset, KTE-C19. Nevertheless, investors seemed happy that it represented a big biopharma endorsement.

The Kite/Amgen alliance essentially targets the identification of novel CAR constructs, for which Amgen will provide new, so-far undisclosed, haematological and solid tumour targets, with Kite leading pre-IND work including cell manufacturing. Amgen paid Kite a $60m signing fee.

Interestingly enough, the tie-up was based entirely on Kite and Amgen’s work, getting around any potential obligation to pay the NCI milestones or royalties. Despite this Kite’s chief executive, Arie Belldegrun, continues to insist that the NCI, Amgen and Kite are in “one partnership”.

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BEYOND CAR-T...

Then there are CAR approaches relating to cells other than T lymphocytes, as well as adoptive cell therapy that goes beyond the use of CARs. Both are set to grow in importance in 2015, especially if realisation spreads that the CAR-T space is overheating in the market.

Already, Conkwest, a company working on CARs expressed on natural killer cells, attracted $48m in private financing in December.

Numerous groups, including the CAR-T players Juno, Kite and Bellicum, are researching T-cell receptor (TCR) therapeutics. The idea behind these is to make T-cells express a specific TCR by use of gene editing; other companies active here are Adaptimmune and Medigene.

Meanwhile, therapy using engineered tumour-infiltrating lymphocytes (TILs) represents another advance that has recently shown signs of coming of age. TIL therapy is the speciality of Dr Steve Rosenberg of the NCI, which has a CRADA covering it with Lion Biotechnologies.

Dr Rosenberg has spoken of what he calls “living treatments” – autologous engineered T-cell receptor-expressing TILs that were tailored individually to a patient’s specific immunogenic mutations. Unfortunately the IP position here is even less clear than in CAR-T therapy.

In any case it is remarkable that, while the past two years have seen work come on in leaps and bounds, it is still the beginning of what might be possible. The TIL approach, for instance, takes personalised medicine to its logical conclusion, creating a new “drug” for each patient.

Follow-on adoptive cell therapies and the sector’s less well-publicised CAR-T companies are set to provide some of the hottest investment themes of 2015. If only safety and cost were no object, biotech bulls would be on to a near-certain winner.

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