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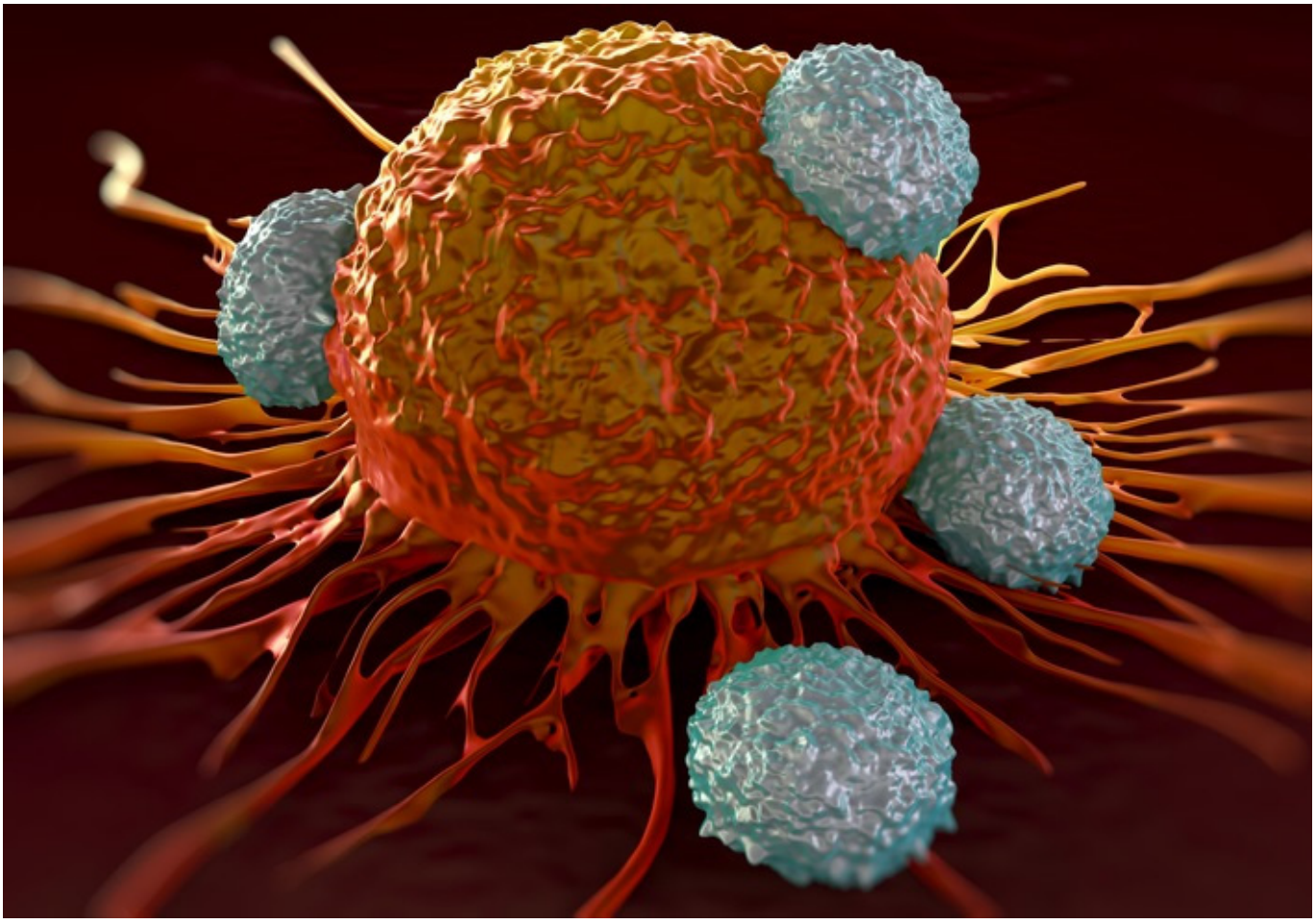

# T-cell cancer therapies: Part 1

## Looking beyond CD19 for the next opportunities

September 2017

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# T-cells and cancers

## Looking beyond CD19 for the next opportunities

Healthcare

27 September 2017

**CD19 CAR-T therapy gives dramatic responses in some B-cell cancers covering 1.4% of US cancers and about 1% of deaths, 6,500. However, the major T-cell therapy opportunities are in MM, AML and major solid cancers with over 1.2m new US cases and 450,000 deaths a year. CAR-T competes in MM and AML but lacks the antigens to attack solid cancers. Celyad's NKR CAR T-cell therapy targets stress antigens with multi-indication potential in AML, MM and solid cancers. The T-cell receptor approach has high specificity and versatility but with specific patient segmentation. Non-cellular therapies (BiTEs and checkpoint inhibitors) could be synergistic.**

## Standard CAR-T – a big but constrained market

Standard CAR-T cell therapy for B-cell cancers (ALL, DLBCL) and multiple myeloma (MM) has a current potential market of 54,000 new cases in the US each year, of which perhaps 19,000 die each year. At the Kymriah US$475,000 price, this market is potentially worth US$9bn. Competition will intensify as multiple companies gain approvals and gear up their manufacturing. To be effective with low side effects, a T-cell therapy ideally needs an antigen target that is abundant on cancer cells and not found on any other cells. This is a very rare set of attributes so CD19/BCMA CAR-T companies cannot diversify directly into solid cancers.

## Multi-cancer NKR CAR T-cell approach emerging

The proprietary natural killer receptor-based (NKR) CAR T-cell approach from Celyad (CYAD-01) targets eight ubiquitous antigens produced by "stressed" cancers as a natural response to genetic damage. NKR CAR could apply to AML, MM and many solid cancers with fewer side effects than CAR-T. CYAD-01 is being trialled in five solid cancer types covering 550,000 new cases and 150,000 deaths a year in the US: a US$75bn potential market. Two haematological cancers (MM and AML) could add up to 52,000 new cases and 23,000 non-responders.

## TCRs, BiTEs and checkpoint inhibitors

T-cell receptor T-cell therapies (TCRs) have exquisite sensitivity. They may target up to 350,000 patients with 91,000 deaths (US$45bn potential market), but their exact markets are limited by segmented tissue type and antigen specificities. In non-cellular approaches, bispecific T-Cell Engagers (BiTEs) may compete in blood cancers but may struggle in solid tumours. Checkpoint inhibitors have efficacy in a few immunogenic cancers and may be best combined with T-cell therapies.

## 53% of development trials target only 10% of patients

While the CD19 CAR-T cell leaders have a big opportunity in B-cell cancers, the other blood cancers like AML and MM and solid cancer opportunities are collectively tenfold greater with huge medical need and less competition. T-cell therapies may revolutionise cancer treatment to benefit patients. Given the major needs in MM, AML and solid cancers, lower response rates will still offer major clinical gains. Currently, 53% of the clinical projects target only 10% of the market. As the leading CAR-T companies face technical struggles to diversify, investors should seek emerging solid cancer opportunities in NKR and TCR CAR T-cells.

### Topics in this report

**Cancer markets of the future**

Antigen challenges

Toxicity risks

Evolving technologies, emerging opportunities

Squeezing future markets

**Haematological cancers**

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Myelomas - a mixed bag

**Solid cancer**

Solid cancer efficacy – differing expectations

Solid tumours – general issues

Preconditioning or shrinking in solid cancers

Can T-cell therapies be mass produced?

**Investment scenarios**

Investment conclusion

**Appendix 1: T-cell therapy terminology**

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TO READ PART 2 OF THIS REPORT CLICK HERE

## Cancer markets of the future

This report looks at three cell-based and two non-cellular approaches to T-cell therapy in cancer, see Exhibit 1. This section, Part 1, summarises the findings and Part 2 (separate) provides detailed technical commentary.

All T-cell therapies use some elements of the natural T-cell receptor, a complex multiprotein assembly that enables the killer T-cells of the immune system kill infected, damaged and foreign cells.

- **Standard CAR-T** uses antibody fragments grafted onto a T-cell Receptor framework to target T-cells to tumour cells. Added costimulatory internal protein domains are needed for potency. A 2016 report from EP Vantage also gives a good overview. These CAR-T therapies need prior chemotherapy (lymphodepletion/preconditioning) to work and this adds cost, toxicity and risk. Specific antigen targets are used, like Novartis's Kymriah (tisagenlecleucel [CTL019]), a CD19 CAR for childhood acute leukaemia, Kite Pharma's axicabtagene ciloleucel (target CD19) in lymphoma and Bluebird's BCMA CAR-T therapy (bb2121) for multiple myeloma. Kymriah is now approved; tisagenlecleucel should follow by the end of November 2017 or earlier. Bb2121 is now in its cohort expansion phase so might gain approval in 2019/2020. Autolus (private UK) uses two CAR-T constructs per T-cell (dual CAR).
- **NKR**, the natural killer receptor CAR T-cell approach used by Celyad (CYAD-01), is potentially very versatile as it targets eight ubiquitous "stress" ligands. The THINK trial underway with CYAD-01 is completing dose-ranging before planned dose expansion into five solid and two blood cancer tumours. CYAD-01 uses an NK receptor and enhanced by linking it to TCR signalling. It is inserted into T-cells. The THINK study does not use preconditioning so CYAD-01 is much less toxic than CAR-T and easier to use. A study in metastatic colorectal cancer is being run alongside standard FOLFOX chemotherapy to explore combination approaches
- **TCR,** the engineered T-cell receptor approach, is championed by Adaptimmune, although other companies, like Kite, have TCR programmes as well. TCR therapy uses protein engineering to enhance the binding strength of a naturally occurring TCR; this means it is not chimeric (as in mixed parts of different proteins). It offers very high selectivity, a TCR feature, but with limited accessible patient populations due to the high specificity of TCRs. TCR therapies often use preconditioning. Trials are at earlier stages compared to CAR-T.

Customised (autologous) T-cell manufacturing has currently limited capacity and costs are very high. Allogeneic technologies might enable mass-market T-cell therapies at lower cost. However, the first clinical CAR-T allogeneic therapy (Cellectis's UCART123) encountered toxicity issues.

Two non-cellular technologies also rely on T-cells for efficacy: Both BiTEs and checkpoint inhibitors (CPI) are engineered proteins.

- **BiTEs** are monoclonal antibodies. A BiTE has two arms and is constructed so that one arm binds a cancer cell antigen while the other arm activates a killer (CD8+) T-cell. There is an approved product, Blincyto. Immunocore uses TCR receptors as one arm.
- **CPIs** like Keytruda have efficacy in only certain tumour types and only in some patients. These are marketed products with clinical trials running to try and extend their approved indications.

Both BiTEs and CPIs may find greater utility combined with CAR T-cell therapies. Both are easier and cheaper to produce than CARs but still have price points around US$150,000.

The therapeutic and commercial development of CARs is affected by two technical factors:

- the availability of antigen targets, which affects technology choice and target indication; and
- additional toxicity risks – any short-term dosing side effects are now mostly manageable.

**Exhibit 1: Technical overview of immunotherapy cellular technologies**

| Name | Basis of the receptor technology | Modifying the receptor to make therapy | What is does | Commentary |
|---|---|---|---|---|
| Standard antibody CAR technology (CAR-T) | Chimeric antigen receptors are modified T-cell receptors. The original T-cell receptor (TCR) has three parts: a complex external domain to recognise non-self and infected cells, a section that crosses the cell membrane and an internal signalling domain (protein section): CD3ζ). | CAR technology is "chimeric" as it uses genetic engineering to replace the TCR domain with an antibody-based binding region. It retains its CD3ζ. Second and third generation CARs add extra co-stimulatory domains (CD28 and or 4-1BB) to enhance the response and persistence. | The CAR genes are inserted into T-cells which makes the new CAR protein. By using an antibody outer the CAR T-cell can be directed to attack almost any cell so long as there is a specific antigen. Once the CAR T-cell binds, it activates the T-cell internal signalling system through CD3ζ to drive the cell killing response. | There are conflicting patent claims on these technologies which might make future commercialisation complicated. For solid cancers, there are no specific cell surface cells so specifically targeting a standard antibody CAR to solid tumours will be difficult with side effect risks. |
| NKG2D natural killer receptor-based CAR T-cell technology (NKR-CAR) | The natural killer group 2D receptor (NKG2D) by natural killer (NK) cells to detect and attack infected and damaged cells, associated co-stimulatory protein DAP10, to activate the NK cell. There are eight known NKG2D ligands (MICA, MICB and ULBP numbers 1-6) produced by damaged, infected or stressed cells. | The NKG2D receptor has no internal signalling domain so a TCR CD3ζ. domain is added to make a CAR. This gives added signalling power. A CAR NKR still binds its normal co-stimulatory molecule DAP10 which is naturally produced by T-cells. This in effect, gives a second-generation CAR. | Cancer cells tend to display one or more of the NKG2D ligands on their surfaces due to being genetically and often metabolically stressed. They are therefore targeted by NKR- CAR T-cells. | The NKR CAR approach needs to establish clear signs of efficacy; there have been three stable disease cases at low doses so far. Preclinical evidence suggests that toxic dose levels are very much higher than those planned in clinical development. The cells show low persistence, preconditioning is not used. In preclinical models, the host (patient) immune system becomes engaged to maintain long-term cancer control. |
| T-cell receptors (TCR) | A TCR is a complex set of interlocked proteins. They detect small fragments of internal proteins displayed in major histocompatibility complex I (MHCI, infective agents are shown in MHCII).– Cancer cells often have mutated or different internal proteins. | A TCR against a known internal cancer antigen is selected. It is then optimised to improve specificity and tested for any cross reactivity. Optimising a TCR is a delicate business. Too low an affinity and efficacy is reduced; too high and the T-cell carrying it deactivates. | A TCR can detect a single mutation in one internal cell protein and unleash the T-cell destructive power as a result. These therefore access a different set of cancer antigens not detectable by standard CAR and NKR CAR. A TCR therapy can also respond to low signal levels. | Every TCR is specific to one MHCI (otherwise called +HLA) type. At best, this is 50% of the population if HLA- A2:02 is chosen. Multiple TCR varieties are needed to cover most of any cancer indication. TCRs occasionally recognise other targets on normal cells although this is not predictable. |
| CAR NK-cells | A CAR-type construct is inserted into harvested natural killer cells. Currently preclinical. | This is the antibody CAR T-cell concept but instead of T-cells, NK cells are used. It has nothing in common with NKR CAR T-cells. | NK-cells, as innate immune cells, are downregulated by "self" HLA molecules on target cells. Cancer cells usually retain some HLAs to prevent NK attack. | NK cells are found in very low numbers in solid tumours. They are hard to culture so getting adequate doses may be difficult. |
| Bispecific T-cell Engagers (BiTEs) | BiTEs are engineered, large antibody-like proteins that are infused into the blood and circulate passively. They have two binding arms. One arm of the BiTE anchors to a cancer cell; the other activates a passing T-cell. There are an enormous number of possible designs. | Products in this report have one CD3 arm to bind and activate a killer T-cell. The other arm can be an antibody-like molecule binding a cancer antigen or a TCR (see below) against internal cancer antigens or even an NK cell receptor like B7-H6. | BiTEs passively rely on itinerant T-cells for efficacy and their ability to access cancer cells embedded in solid tumour masses is uncertain. The choice of antigen bound by the other arm also determines efficacy and side effects and here the paucity of antigen choice has limited commercial development. | Like anti-cancer monoclonal antibodies, they are maybe of most use in haematological cancers; preclinical evidence suggests utility in some solid tumour types. Large pharma seems to be investing in these as they fit into their development and commercial structures. |
| Checkpoint inhibitors (CPI) | These are a range of approved therapeutic antibodies designed to overcome immune tolerance to cancer. | A CTLA-4 inhibitor allows a T-cell response to develop. Other checkpoint inhibitors bind either the programmed cell death (PD1 receptor) or Programmed cell death Ligand (PD-L1). Blocking PD1/PD-L1 stopping T-cells that recognise a cancer "self" target from being killed. | Checkpoint inhibitors have no specific targeting mechanism but rely on lowering controls on the immune system sufficiently to overcome tolerance against the cancer. If doses are too high, they allow direct attack by the immune system on healthy tissues. | One CTLA-4 (Yerovoy, ipilimumab ) and various PD1 antibodies, Opdivo (Nivolumab), Keytruda (pembrolizumab) are approved for various cancers. PDL-1 inhibitors include Tecentriq (atezolizuma) Bavencio (Avelumab) and Imfinzi (Durvalumab). Non-small cell lung cancer, bladder cancer and melanoma are the main markets. |

Source: Edison Investment Research

## Antigen challenges

To be effective with low side effects, a T-cell therapy ideally needs an antigen target that is abundant on cancer cells and not found on any other cells. This is a rare set of attributes. The lead CD19 antigen target is not cancer specific; it also kills healthy B-cells so patients cannot make new antibodies and need supplemental injections.

The problem of which antigen to target will limit the transition of standard CAR T-cell therapies into solid tumours. The types of antigens accessible to the different technologies are shown in Exhibit 2.

**Exhibit 2: Types of antigens and technologies suitable to target them**

| Type | Comment | Cancer cells | Heathy cells | Technology | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | CAR-T | NKR | TCR | BiTEs | CPI |
| Cancer antigens | These are normal proteins and not recognised by T-cells | Found at high levels on tumours originating in a specific organ | Found at low levels on related tissues | Yes | No | No | Yes | No |
| Stress ligands | NK receptors like NKG2D recognise eight possible ligands | Produced by cancer cells as part of genetic damage response | No unless damaged, infected or inflamed | No | Yes (NKG2D) | No | Yes (B7-H6) | No |
| Internal antigens | Internal cell proteins, usually fetal, made only by cancers in adults | Peptide fragments are shown on cell's surface in MHCI (HLA) | No (unless a specialist tissue, eg gonads) | No | No | Yes | Yes if TCR arm | Possible |
| Mutated genes | Random, unrepaired genetic damage due to UV light or toxins | Patient-specific peptide fragments are shown on cell's surface | No | No | Yes | No | No | Yes |

Source: Edison Investment Research

## Toxicity risks

Antigen specificity is linked to toxicity and side effects, Exhibit 3. These are separate from the generally manageable side effects of cytokine release and neurotoxicity associated with standard CAR-T and TCR dosing – although these can still be fatal if not controlled. NKR CAR dosing is different and has not shown short-term side effects to date.

**Exhibit 3: On and off target effects**

| | On target | Off target |
|---|---|---|
| **On tumour** | This is the aim of the therapy: a specific antigen on a tumour is effectively targeted, delivering cancer cell killing and potential cure. CAR constructs can be engineered to be very strongly binding giving powerful responses. NK receptors already have strong ligand binding. | An aim of all modified T-cell therapies is to get antigen spreading to give lasting immunity. Preconditioning by damaging and degrading the existing immune system may make this harder to achieve. Checkpoint inhibitors rely on this effect as they are not targeted. |
| **Off tumour** | The tumour antigen is also present at lower levels on healthy tissue, meaning that the therapy kills healthy cells. This can lead to attacks on other organs that can be difficult to control, cause damage or be fatal. | This is a potential, sometimes fatal, side effect. It is mostly a risk in TCR development, but is a concern for any approach. It means that initial clinical studies are cautious and dose ranging. |

Source: Edison Investment Research

Toxicity is a real risk. In early studies, a TCR therapy recognised heart muscle in preference to the targeted tumour cells and caused rapid cardiac failure and death in two patients (see Part 2 for details). There have been brain side effects in standard CAR-T therapies against melanoma. A standard CAR against colorectal cancer caused lung failure and patient death. The JCAR015 trial caused five toxicity deaths. Cellectis had to halt trials after serious toxicities in the first two patients, one died. Developers have learnt from these setbacks but the risks are still present.

Basically, there are four outcomes, Exhibit 2. Developers seek "**on target, on tumour**" specificity so the CAR therapy directly attacks the tumour cells using the designated antigen target. They also want "**off target, on tumour**" effects, that is the tumour is still targeted but by new tumour antigen targets detected by the host immune system. If this happens, it gives a longer-lasting immune response, as can happen with checkpoint inhibitors. This enables the immune system to act effectively against the cancer and generate potentially long-term immunity. NKR CAR T-cell therapy is designed to try to generate such a response as seen in preclinical work.

The risks come from off tumour targeting against healthy tissues. As a T-cell therapy is alive – the transformed T-cells grow, and die – the cell dose given does not necessarily correlate with efficacy and CAR T-cells could persist for years, even if undetectable, but react later. This is unlike small molecule therapeutics where the dose is known and the molecule is degraded or excreted quickly.

The particular risk limiting standard CAR and BiTEs (also checkpoint toxicities) is "**on target, off tumour**" toxicity. This is a known side effect of CD19 therapy where healthy B-cells are also killed so patients cannot make antibodies against infections; this can be managed clinically. It is a theoretical risk in NKR therapy in case of infection or inflammation that might "stress" cells.

The major concern for TCR approaches is unexpected "**off target, off tumour**" effects; that is, the modified T-cells react against a different target on healthy tissue. This should be a rare event but it can occur and has been fatal. TCRs should otherwise be highly specific therapies.

## Evolving technologies; emerging opportunities

A comparison of the top-line potential patient numbers and medical need against activity shows the current balance between haematological and solid cancer development, Exhibit 4. This looks at US incidence (patients diagnosed per year) as a measure of the overall US market.

**Exhibit 4: Technologies and patient numbers**

| Cancer indication | Incidence | Mortality | Five-year survival | Technologies and antigens | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Standard CAR-T | | | Other CAR T-cell | | Monoclonal | |
| | | | | CD19 | BCMA | Other | NKR CAR | TCR | BiTE | CPI |
| **CD19 targeted cancers** | | | | | | | | | | |
| ALL | 5,970 | 1,440 | 68.2% | ■ | | ● | | | ■ | |
| CLL | 20,110 | 4,660 | 83.2% | ● | | | | | ● | |
| Hodgkin lymphoma | 8,260 | 1,070 | 86.4% | ● | | | | | ● | ■ |
| NHL | 72,240 | 20,140 | 71.0% | □ | | ● | | | | |
| (DLBCL subgroup) | (18,560) | (5,000[1]) | (NA) | | | | | | | |
| Total lymphoid | 106,580 | 27,310 | | | | | | | | |
| % total cancers | 6.31% | 4.54% | | | | | | | | |
| Of which ALL & DLBCL | 24,530 | 6,070 | | | | | | | | |
| % total cancers | 1.4% | 1% | | | | | | | | |
| **Other haematological cancers** | | | | | | | | | | |
| Multiple myeloma | 30,280 | 12,590 | 49.6% | | ● | | ● | ● | | |
| AML | 21,380 | 10,590 | 26.9% | | | ● | ● | ● | ● | |
| CML | 8,950 | 1,080 | 66.0% | | | | | | | |
| Total Other | 60,610 | 24,260 | | | | | | | | |
| % total cancers | 3.59% | 4.04% | | | | | | | | |
| All haematological | 167,190 | 51,870 | | | | | | | | |
| % total cancers | 9.90% | 8.58% | | | | | | | | |
| **Major solid cancers** | | | | | | | | | | |
| Head and neck | 49,670 | 9,700 | 64.5% | | | | | ● | ● | |
| Melanoma | 87,110 | 9,730 | 91.7% | | | ● | | ● | | ■ |
| endometrial (uterus) | 61,380 | 10,920 | 81.3% | | | | | | | |
| Stomach (gastric) | 28,000 | 10,960 | 30.6% | | | | | | ● | |
| Ovarian | 22,440 | 14,080 | 46.5% | | | ● | ● | ● | | |
| Kidney | 63,990 | 14,500 | 74.1% | | | | | | | |
| Brain | 23,800 | 16,700 | 33.6% | | | ● | | | | |
| Bladder | 79,303 | 16,870 | 77.3% | | | | ● | ● | | ■ |
| Prostate | 161,360 | 26,730 | 98.6% | | | | | | | |
| Liver | 40,710 | 28,290 | 17.6% | | | | | ○ | | |
| Breast | 252,710 | 40,610 | 89.7% | | | ● | ● | | ● | |
| Pancreas | 53,970 | 43,090 | 8.2% | | | | ● | | | |
| Colorectal | 135,460 | 50,260 | 64.9% | | | | ● | | ● | |
| Lung | 222,500 | 155,870 | 18.1% | | | ● | | | | ■ |
| Solid cancer as listed | 1,282,403 | 448,310 | | | | | | | | |
| % total cancers | 75.9% | 74.6% | | | | | | | | |
| **All US cancers** | 1,688,780 | 600,920 | 67% | | | | | | | |

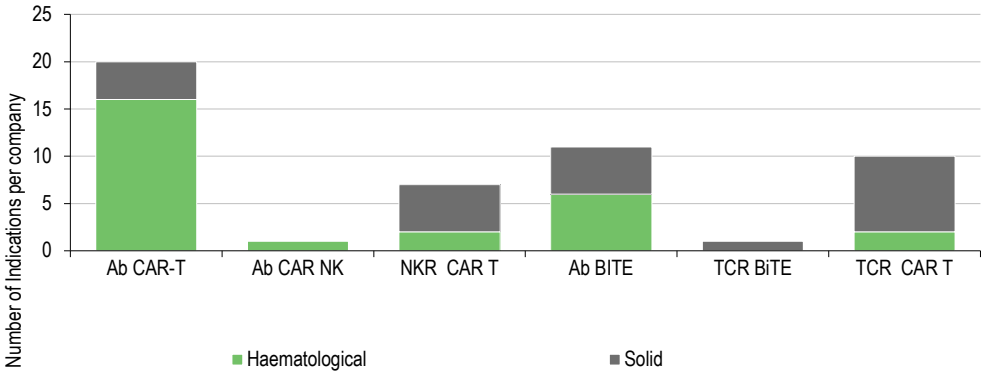
Source: Edison Investment Research. Key: ●= current clinical indication, ○= possible or preclinical indication, ■= approved (or □ = expected) indication. Organised by number of deaths based on US SEER data.

[1] Edison has not established a specific figure for DLBCL deaths so assumes 25% for illustrative purposes. Survival is already very good with R-CHOP therapy (Rituxan with combination chemotherapy). Follicular lymphoma is also a major possible indication but as a slowly developing, indolent, cancer subtype of NHL, may be less relevant commercially for CAR-T therapies.

The US is assumed by Edison to be at least 75% of the immediate global market due to the cost of these therapies. Medical need is indicated by five-year survival rates (SEER data). The number of deaths is a good proxy for the relapsed/refractory patients in whom these therapies will be first approved and which are likely to be reimbursed. The likely market potential will be between the number of new cases suitable for the therapy (maximum sales potential if first line therapy) and the number of deaths (the potential as relapsed and refractory therapy). The sales then depend on efficacy, production levels and price. It is likely that patients will want the most effective therapy first.

The distribution of commercial projects between haematological and solid tumour indications is shown in Exhibit 5. Note that this excludes related academic studies, apart from Juno Therapeutics, where the corporate policy seems to be to outsource many early clinical developments. Chinese studies are also excluded from this US-centric analysis. The balance between haematological and solid cancers in terms of indications being clinically developed by companies is about 55% haematological and 45% solid. As of September 2017, 54% of the indications in development by various companies target under 6% of the overall potential market (Exhibits 5 and 4). However, many solid cancer studies are still exploratory and small, so may not proceed to pivotal studies. In haematological cancers, companies are developing new products but also running line extension studies to broaden their expected initial labelling.

**Exhibit 5: Clinical-stage projects (September 2017) using CAR and TCR approaches**

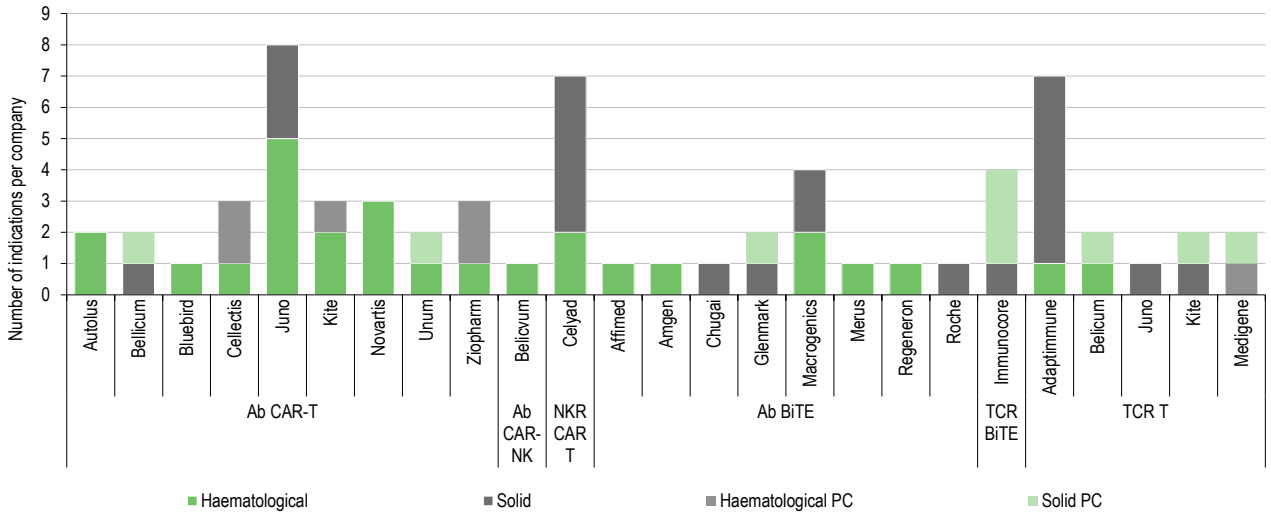



Source: Edison Investment Research based on clinical trials.gov and company websites 7 September 2017.
Key: Ab CAR T = standard CAR T-cells; Ab CAR NK = standard CAR NK cells; NKR T = NKG2D receptor CAR T-cells; Ab BiTEs = bispecific T-cell engagers using antibody and CD3 arms; TCR BiTEs = TCR arm and CD3 BiTE; TCR CAR T = T-cell receptor.
Note: Indications per company per technology and antigen counted but some companies have several trials in the same indication (eg Kite in with CD19 CAR-T in NHL) so are counted once. Multiple indication dose ranging studies count once unless clear intention to run cohort expansion phase subsequently.

The data in Exhibit 5 are split into companies in Exhibit 6. Some companies appear in more than one section, for example, Kite is focused on CD19 CAR-T for DLBCL and ALL but has a TCR trial.

The biggest group of commercial western developments are clearly in haematological cancers and standard CAR-T largely CD19 and BCMA projects. Here, Novartis and especially Kite dominate with tight CD19 focus in getting product to market. Kite is being acquired by Gilead for US$ 12bn showing increased big pharma interest. Juno has a broader, strategy targeting CD19 and BCMA indications; plus CD22 as a haematological target. Juno is also looking at solid cancer CAR-T technology with three trials and it also has a TCR. Bellicum has a pancreatic cancer study underway. It also has an exploratory trial running with umbilical-derived NK cells (rather than T-cells) transformed with a CD19 CAR. Bluebird has the lead in multiple myeloma as its bb2121 BCMA targeted CAR T-cell therapy has moved into dose expansion. Autolus has two trials running using two CAR-T constructs per cell for DLBCL, paediatric ALL and MM. The idea is that cancer cells display a range of ligands so using a combination of ligands improves cancer targeting and reduces the risk of cancer escape by loss of a single antigen.

**Exhibit 6: Company clinical and later-stage preclinical projects by technology and indication**




Source: Edison Investment Research based on clinical trials.gov 7 September 2017. Key as Exhibit 4. PC = interesting preclinical project.

Natural killer receptor-based CAR T-cell technology, owned by Celyad, is nearing the completion of its dose escalation phase of the THINK trial and is expected to move into an expansion phase with evaluation of seven different cancer types using a high standardised repeated dose: two haematological and five solid indications. This trial should be in a cohort expansion phase during 2018 so we expect clearer efficacy data to emerge.

The SHRNK study looks at NKR-CAR T-cell therapy in colorectal cancer and chemotherapy; it is not separately counted. It is however, a very important study as it will evaluate how to use T-cell therapy in the real world of solid tumour treatments. Most solid cancer patients will receive chemotherapy and learning how to use these combinations for maximum efficacy is very important.

In TCR CAR T-cells, the majority of trials are Phase I/II trials from Adaptimmune; a synovial sarcoma product is most advanced. Adaptimmune has two current TCR antigens under investigation (NY-ESO-1 and MAGE A10); a third antigen (MAGE A4) may enter trials in 2017. TCRs require multiple products to access different patient subsets but the same product can be used in different indications. Juno is supporting an academic sponsored study in NSCLC, a trial in AML was suspended. Medigene plans to start a TCR-based trial in 2017 so is included in this analysis. Bellicum has a haematological TCR trial running in pancreatic cancer and a melanoma trial planned.

A diverse set of trials are evaluating bispecific antibodies. No company dominates this field but Macrogenics is running a multi-indication dose ranging study on its B7-H3 antigen BiTE (counted as one trial) plus a specific colorectal study with gpA33. It also has CD19 and CD123 haematological studies. There are some major players (Amgen, Roche) plus new entrants (like Indian company Glenmark Pharmaceuticals) and the advantage of an approved, if limited indication, product. Commercially, these are mass-market products if good efficacy is obtained.

Immunocore is separately categorised as a hybrid TCT and BiTE approach. The trials listed as underway with IMCgp100 are all in melanoma including the small eye (uveal) melanoma indication and in a combination with checkpoint inhibitors for skin melanoma. There are preclinical indications.

## Squeezed future CAR-T markets?

As the haematology CAR market matures, there may be several companies chasing a relatively small pool of eligible, funded patients as companies diversify from their initial approved indication

into other cancer types, a classic commercial strategy. This could create a few winners, with strong therapies and pricing, but perhaps more losers with small volumes and very high fixed overheads. A small haematological market could be stable and profitable while there is limited autologous production capacity. However, in future, as manufacturing issues are resolved and if overcapacity develops – or if allogeneic therapy becomes mainstream – pricing could become highly competitive. BiTEs might take haematological market share at a lower cost, although Blincyto, the first approved product, has limited use: 2016 sales were US$115m.

The lack of clear antigens to target with standard CAR therapy (Juno's exploratory efforts aside) leaves the solid cancer market to the other two CAR T-cell therapies in clinical development: NKR and TCR.[2] Both offer selectivity against solid cancers vs healthy tissues; standard CAR will struggle to achieve this. Both NKR and TCR are looking to compete in some haematological indications.

NKR CAR technology is potentially more versatile than TCR as the NKR ligands are ubiquitous. This means that the same NKR viral construct could be used across multiple cancers. In addition, Celyad, developing NKK therapies, has a strong patent position in allogeneic therapies. This may be a major advantage in opening up mass-market sold cancer therapy.

TCR applicability is much more segmented depending on the exact internal cancer antigen produced by the tumour and the exact patient tissue type. Once those match, the therapy can in theory be used with any cancer. The HLA (tissue type) A2 is carried by about half the population so is often targeted. Different antigens have different expression levels in different tumour types. So if the internal cancer antigen that is found in half the instances of a particular cancer indication was targeted by an A2:02 TCR, the T-cell therapy would address 25% of the potential market.

[2] There are multiple standard CAR therapies against many varied surface cancer antigens targets being trialled in China. If any of these finds a reliable route to use standard CAR-T in solid cancers, then the situation will be more competitive, but every standard CAR-T needs a new antigen per indication and a full development project. Chinese products will presumably also need US studies and manufacturing.

# Haematological cancers

Haematological cancers vary depending on the severity of the condition, the type of blood cell they originated from and the location where the cancer originated. Acute forms are immature and more aggressive; chronic forms are more mature and slower growing. For targeting CAR-T, the main difference is the originating cell type. Lymphoid cancers are from cells that make antibody producing B-cells and T-cells. Myeloid cancers are from cells that make other white cell types and red blood cells and platelets. Finally, leukaemias originate in the bone marrow and lymphomas originate in tissues like lymph nodes. Multiple myeloma, to be complicated, is a bone marrow cancer of mature antibody producing cells so is lymphoid in origin. All therapies against these cancers are potentially a bridge to stem-cell transplant which provides a cure, if successful.

## CD19 CARs – the exceptional niche market

Most current CAR development, largely CD19 antigen targeting, is focused on the lymphoid haematological segment and mainly ALL and DLBCL. Juno also targets CD22 with JCASR018 and there is a dual CAR-T from Autolus targeting both CD19 and CD22.

The June 2017 Kymriah data (in patients who were previously ineligible for a stem cell transplant) indicate a 12-month relapse-free probability of 64% but this is a preliminary estimate.

Based on incidence, there are 106,000 new lymphoid cancers each year with 27,000 deaths (excluding MM). This includes CLL and all NHL patients but, so far, CD19 targets just ALL and about 25% of NHL patients, those with DLBCL. Counting ALL and DLBCL only, there are 24,000 new cases and perhaps 6,500 deaths a year in the US on a simplistic basis. DCBCL is well treated with rituximab, a CD20 monoclonal and combination chemotherapy. At a proposed US$475k per treatment,[3] the current addressable US potential market is about US$3bn (plus associated medical costs and any additional follow-on stem cell transplants at up to $800k each).

Given the number of potential competitors in ALL and DBCL and the high fixed costs of autologous cell manufacturing, this could be a very crowded and fierce market. Market expansion depends on moving to first line therapy and replacing some stem cell transplants. Patients may try to opt for first line CAR T-cell therapy as a bridge to transplant rather than chemotherapy with its side effects; this could expand the US market significantly. Clearly, prices will have to fall to make standard first line use affordable, even in the US.

Production of autologous CAR-T therapies is an important issue. Kite Pharma has disclosed that its production facility (excluding viral vector production) has a 4,000-5,000 unit capacity. Novartis has a large facility of unknown capacity. This is sufficient for the relapsed/refractory B-cell indications currently addressed but additional uses could strain supply.

If allogeneic therapies allow a much higher production capacity at lower cost, the competitive situation could become tougher; the Cellectis UCART123 allogeneic setback might push this back as the trial halted after high toxicity and one death in the first two patients. Novartis has licenced Celyad's allogeneic technology so potentially allowing capacity expansion. Note that manufacture of CAR-T cells needs manufacturing grade virus. This is only available from a few suppliers and manufacturing is still laborious. Viral supply might be a major limitation for some years.

BiTEs might be competitive against CARs in the haematological market as they have CAR-like action. An approved BiTE Blincyto (blinatumomab) is approved for second line ALL and BiTEs are being developed for all these indications. Pfizer has FDA approval for Besponda (inotuzumab ozogamicin), a conjugated anti-CD22 monoclonal, for relapsed or refractory adult ALL. This is not a

[3] Novartis has offered that the therapy is free is there is no response with 30-days.

T-cell therapy. It does not show an overall survival advantage over current therapies although it does offer more patients a bridge to transplant.

## Other haematological cancers - a greater opportunity

We have classed multiple myeloma (MM) and acute and chronic myeloid leukaemias in this category. Clinically, MM is a cancer of lymphoid origin plasma cells: mature B-cells. Plasma cells do not display CD19 so other targets are needed. This has enabled a more varied range of products to enter development. Of the two myeloid cancers, relapsed /refractory AML is intractable but an interesting market and CML is already well treated. These cancers together offer a bigger market than the B-cell cancers addressed by current CD19 CAR-T therapies.

### Multiple myeloma

Multiple myeloma (MM) has effective chemotherapy treatments like bortezomib (Velcade) but five-year survival is still only 49%. Where possible, patients receive stem cell transplants. Bluebird has reported good initial results in a standard CAR trial with a B-cell maturation antigen target (BCMA) and is in cohort expansion pivotal trials. Celyad is running an NKR CAR T-cell trial in MM, currently in dose ranging. Adaptimmune has a TCR trial running. The potential MM market is possibly US$15bn based on the incidence of up to 30,000 cases per year and the theoretical US$0.5m price point used earlier. However, based on relapsed cases alone, the market is about 13,000 cases, still US$6.5bn. Autolus has a dual CAR-T therapy trial in multiple myeloma targeting BCMA and TACI.[4]

### Myelomas

The two myeloid leukaemias: acute (AML) and chronic (CML) are relatively minor markets.

- CML with about 1,000 deaths per year is treated with inhibitors like Gleevec (imatinib), now generic, Bosutinib (Bosulif) Sprycel (dasatinib) and Tasigna (nilotinib). There are no T-cell studies in CML. This does not prevent future line extension studies.
- AML, a larger but varied condition has 21,000 patients per year. First line therapy responsive AML patients get stem cell transplants. Unresponsive patients (r/r) have further chemotherapy. There are 11,000 deaths with a high medical need. AML is a popular indication for clinical trials, with 508 active studies ongoing as of August 2017, of which 107 were industry funded. There are two western CAR-T studies run respectively by Ziopharm with MD Anderson (CD33) and Cellectis (allogeneic CAR targeting CD123 but on hold). Celyad (NKR CAR) is in dose ranging studies. Other studies are being run in China. r/r AML is very unresponsive to therapies.

If any T-cell therapy is effective in relapsed and refractory AML, this should be a good market that is we estimate could be worth over US$5bn at the theoretical US$0.5m price point used earlier given the lack of alternatives. Pfizer looks likely to gain a fresh approval for Mylotarg (gemtuzumab ozogamicin), an anti-CD33 targeted conjugated monoclonal approved in 2000 and withdrawn in 2010. This might complicate future markets but T-cell therapy could be more effective.

[4] Transmembrane activator and calcium modulator and cyclophilin ligand interactor.

## Solid cancers

Solid cancers are among the most common and lethal diseases and remain one of the most intractable problems in modern medicine. There are nearly 1.3m new solid cancer cases per year in the US based on SEER data, Exhibit 4. Some solid cancers, like pancreatic cancer, have seen little progress in patient survival for decades. Many therapies are old and ineffective but still extensively used. The best treatment remains early surgical removal, but many cases are found too late.

Standard CAR-T therapies are being extensively developed in China but not in the US. The reasons (as above) relate to the lack of a clear cancer antigen target for the antibody fragments used. This has resulted in toxicities in earlier western trials. It is indicative that Kite Pharma has started a TCR T-cell trial in sold cancer; Juno also has a TCR programme.

Celyad's NKR CAR T-cell approach (CYAD-01) uses ubiquitous stress ligands seen commonly on cancer cells but not seen on healthy tissue. NKR CAR can target potential multiple cancer types with one viral construct. This will speed up development of multiple indications if efficacy is seen. The THINK study (currently in its dose escalation stage) will evaluate Celyad's lead therapy, CYAD-01, in ovarian, bladder, triple negative breast cancer, colorectal and pancreatic cancers. These are much bigger potential markets than CD19 in haematology and with less competition and greater medical need. On a simple assessment, NKR CAR could address about 274,000 US patients with about 165,000 deaths, Exhibit 7.

**Exhibit 7: NKR solid tumour targets in THINK study**

| | Unadjusted | 5-year survival | Adjustment | Adjusted | Deaths | Notes |
|---|---|---|---|---|---|---|
| Ovarian | 22,440 | 46.5% | 100% | 22,440 | 14,080 | Many detected only at a late stage so high mortality and high need |
| Bladder | 79,303 | 77.3% | 100% | 79,303 | 16,870 | Known to be immunogenic, combine with CPI? |
| Breast | 252,710 | 89.7% | 15% | 50,542 | 40,610 | Triple negative tumours are 10-20% of cases with 77% 5-year survival |
| Colorectal | 135,460 | 64.9% | 50% | 67,730 | 50,260 | About 50% of new cases are non-metastatic |
| Pancreatic | 53,970 | 8.2% | 100% | 53,971 | 43,090 | Any significant advance in this cancer would be a breakthrough |
| | **543,883** | | **100%** | **273,986** | **164,910** | |

Source: SEER data. Note: Breast cancer incidence adjusted by proportion of triple negative patients. Colorectal incidence adjusted approximately to exclude early stage diagnoses curable by surgery.

TCR therapies are being tested in various solid cancers by a variety of companies including Kite, Juno, Bellicum and especially Adaptimmune. It is harder to estimate the potential patient coverage for TCRs as they recognise specific tissue type and then only work if the cancer displays a specific antigen; what proportion of cells need to show the antigen is not certain to get the widespread immune response needed. Their huge advantage is that they detect internal cancer antigens. No other technology does this. This means they particularly focus on fetal antigens like NY-ESO-1, PRAME or the MAGE series of antigens. These antigens found in many tumour types.

For example, in multiple myeloma, a trial is recruiting HLA A2 – up to 50% of the population, then checks for NY-ESO-1 or the related LAGE-1a proteins. These occur in about 34% of MM cases with LAGE-1a twice as common. With 12,500 multiple myeloma US deaths annually, the market is potentially 2,140 cases. At US$0.5m as a price point, that is a US$1bn market. This could double if used as first line therapy. The big advantage is that by specifying patients, competition might be limited. However, this depends on showing excellent efficacy. If efficacy is similar, the therapy has more competition but fewer potential patients and possibly higher overhead costs.

Although estimates of specific internal cancer antigen levels vary in the literature, Exhibit 8 shows possible market segmentation based on Adaptimmune's current clinical portfolio. All are based on HLA A2:02 variants. This shows that of about 500,000 possible refractory cases (deaths), about 100,000 could be eligible for therapy. At the US$0.5m price assumption, this would represent a potential US$45bn market. Adaptimmune has partnered with GSK on some projects.

**Exhibit 8: Eligible patient segments for specific TCR therapies in Adaptimmune trials**

| Indication | HLA | % | Antigen | % | Deaths | Potential | Nominal value |
|---|---|---|---|---|---|---|---|
| Multiple myeloma | A2 | 47% | NY-ESO-1 | 34% | 12,590 | 2,029 | 1,014.5 |
| Head and neck | A2 | 47% | MAGE-A10 | 33% | 9,700 | 1,517 | 758.5 |
| | | | MAGE-A4 | 42% | 9,700 | 1,931 | 965.5 |
| Bladder | A2 | 47% | MAGE-A10 | 31% | 16,870 | 2,479 | 1,239.5 |
| | | | MAGE-A4 | 34% | 26,730 | 4,308 | 2,154.0 |
| Non-small cell lung (NSCLC) | A2 | 47% | MAGE-A10 | 22% | 132,490 | 13,816 | 6,908.0 |
| | | | NY-ESO-1 | 33% | 132,490 | 20,724 | 10,362.0 |
| | | | MAGE-A4 | 60% | 132,490 | 37,680 | 18,840.0 |
| Ovarian | A2 | 47% | NY-ESO-1 | 19% | 14,080 | 1,268 | 634.0 |
| | | | | | **487,139** | **85,752** | **42,876.0** |

Source: Edison Investment Research and cancer epitope numbers sourced from Adaptimmune corporate presentation July 2017 or literature. Note: NSCLC is 85% of overall lung cancers but is segmented into different cell subtypes and expression levels of antigens.

# Solid cancer efficacy – differing expectations

As yet, the efficacy of T-cell therapies in solid tumours is not known but it is unlikely that a solid cancer will respond in the same way as haematological CD19 cancers. For example, the Novartis ELIANA study in ALL found that 83% of patients responded to Kymriah within three months. Adaptimmune reported a 91% response rate in a TCR multiple myeloma study in 22 patients at day 100 (this was a narrow indication after autologous stem cell transplants).

Given the major need in solid cancers, lower response rates still offer worthwhile clinical gains. Keytruda, the marketed checkpoint inhibitor, given with chemotherapy for non-small cell lung cancer (NSCLC) gave a 55% partial response vs 29% on chemotherapy alone, seen as a strong result. Immediate responses do not necessarily translate into prolonged survival. A more robust metric will be overall survival, but such data could take years to produce. Responses will also vary with cancer type and medical need. For example, any improvement in pancreatic cancer would be a major advance; Celyad has published some promising preclinical pancreatic data so the THINK Phase II output will be very interesting.

In NKR CAR T-cell therapy, Celyad has noted a potential response in an AML patient at a low single dose in an earlier study. In the current THINK study, there have been two stable disease cases in metastatic colorectal cancer at the lowest dose level with three CYAD-01 doses given.

Kite Pharma has reported on a TCR dose escalation study (run by the USA National Cancer Institute (NCI)) in advanced cancers seeing three patients of nine (30%) at the target dose show tumour regression; another patient with cervical cancer had a complete remission at a lower dose. Evidence to date indicates that cellular therapy responses are not tightly correlated with received dose or cell quality; this was noted by Novartis in its Kymriah FDA filing.

## Solid tumours – general issues

For all T-cell approaches, solid tumours are a much more difficult target. There are a range of other issues whose relevance is not fully understood clinically, Exhibit 9.

**Exhibit 9: Major issues in solid tumour therapy development**

| Issue | Technical factors | Comment |
|---|---|---|
| The need for infused, modified T-cells to find tumours | T-cells home in on chemical signals, chemokines. Lack of these could be a factor in non-responding patients but sophisticated tests will need to be aware of this as a limitation. | T-cells naturally access and infiltrate tumours especially if attracted by chemical signal: cytokine and chemokines. Not all tumours will secrete the right signals to attract the CAR T-cells used. The direct approach is to inject the modified T-cells directly into the tumour. This obviously depends on the surgeon being able to locate and access the tumour so is restricted to superficial tumour masses. |
| T-cell infiltration of tumours | Tumour blood vessels are narrow and very convoluted. This makes it difficult for T-cells and larger proteins to access them. Tumours have a high internal pressure. This is a physical barrier to any T-cell moving into the tumour. Tumours are composed of cells imbedded in extracellular matrix, a composite of sugars and proteins. | T-cells use adhesion molecules to anchor themselves against tumour pressure and are clearly observed in tumours. T-cells can enzymatically dissolve the tumour matrix to move into and through the tumour and access cancer cells. Pressure will limit the concentration of large proteins like BiTEs in the tumour mass. |
| The need to overcome Treg and TFGβ immune suppression | There are multiple soluble signalling factors which can supress T-cell killing activity. Regulatory T-cells and tumour cells secrete transforming growth factor beta (TFGβ) to supress T-cell activity. | Tregs can be ablated by preconditioning so enabling a CAR T-cell tumour attack. Adaptimmune is using preconditioning for TCR therapy.<br>Tregs also express NKR ligands so may be eliminated by NKR CAR T-cells.<br>Juno has "armoured" CARs which secrete IL12 to simulate immune attacks.<br>SPEAR technology (Adaptimmune) adds soluble TFGβ receptor genes into modified TCR cells to block TFGβ suppression of activity. |
| Checkpoint ligands downregulate T-cells | Cancer cells often express checkpoint ligands that stop T-cells from becoming activated. | Combinations of CAR-T therapy and checkpoint inhibitor therapies are already being explored. |
| Low amino acid level in tumours | Tumours are thought to alter the local concentration of the amino acid tryptophan. This can slow T-cell activity. An animal model where this activity was blocked responded to T-cells whereas in tumours retaining it, the T-cells failed to control the cancer. | This is an often-stated theory but natural blood tryptophan levels are high so the effects need to be very localised for this to apply in a clinical situation. This is possible inside a tumour with a very poor blood supply. Preconditioning, by attacking tumour cells, is claimed to reduce this effect in animal models. However, this will depend on the tumour and chemotherapy. |
| Lack of oxygen (hypoxia | The interior of solid tumours have poor blood supply and low oxygen levels, which impairs T-cell function. Low oxygen also leads to a very acidic local environment, again hostile to T-cells. | CAR-T and TCR therapies can do little on this. BiTEs will have trouble penetrating poorly vascularised tumours. NKR could have an advantage as tumour vasculature becomes stressed generating NKR ligands enabling them, in preclinical models, to be targeted by NKR CAR T-cells: anti-angiogenic action. |

Source: Edison Investment Research, Newick et al (2016)

Companies are already starting to test ways to prevent some of these escape mechanisms. This might be a direct injection of modified T-cells into tumours, where accessible, or sophisticated molecular biology like using decoy receptors to remove signalling molecules that deactivate T-cells Adaptimmune SEAR technology). Without more clinical data, the relevance of these factors cannot be fully assessed.

## Preconditioning or shrinking in solid cancers

Preconditioning (chemotherapy with cyclophosphamide and fludarabine) is essential for haematological cancers. It is given before CAR-T and TCR T-cells are given to deplete the host immune system. This allows the CAR-T and TCR T-cells space to expand (grow) and removes host Tregs that might restrict such growth. It also attacks the blood tumour cells. Preconditioning allows fast expansion of CD19 CAR T-cells, perhaps 1,000 fold or more compared to the dose given, but causes toxicities like cytokine release syndrome and neurotoxicity. This requires careful (and expensive) hospital observation and the ability and expertise to intervene rapidly to manage any toxicities. These toxicities have not been fully overcome and can still be fatal.

NKR CAR T-cell therapy does not use prior preconditioning so no fast growth of the NKR CAR T-cells happens. Instead, Celyad gives three equal doses of CYAD-01 over three weeks. So far, no toxic responses have been seen. The aim is to attack the tumour and its vasculature so that a host immune response is generated against the cancer. This should give a more sustained, but less dramatic clinical response.

Celyad is starting the SHRINK study in metastatic colorectal cancer which will give NKR CAR therapy after FOLFOX chemotherapy. FOLFOX will only marginally affect the patient's immune system but should shrink the tumour mass and might enhance NKR efficacy by generating a higher level of cancer stress ligands. This risk is that healthy cells may also have a residual stress response apparent when NKR CAR T-cells are infused which could lead to toxicities. The wash out and recovery period needed is therefore a focus of the SHRINK study. This will be an interesting trial and essential if NKR therapy is to be combined with traditional chemotherapy.

TCR T-cell approaches currently use preconditioning. This enables the TCR T-cells to expand (we assume), but in general the chemotherapy that ablates the patient's immune system will not strongly affect solid tumours. Therefore, only half of the potential preconditioning benefits gained in haematological cancer are potentially obtained in solid cancers. More data is needed to fully assess this aspect.

## Can T-cell therapies be mass produced?

T-cell therapies are mostly autologous, that is, T-cells are extracted from the patient's blood, sent to a central facility and then transformed into therapeutic cells by use of highly controlled viral insertion into the T-cell genomes. This can take up to a month. Cells are then returned to the donor patient for use.

Manufacturing of all T-cell therapies remains a major challenge. Techniques to produce the viruses needed to transform isolated patient T-cells are small scale, very manual and have limited capacity. There are two viral types: lentivirus (based on HIV but with all harmful genes removed) and retrovirus, an older but effective technology. Novartis uses lentivirus, Celyad uses retrovirus. Suppliers like Oxford BioMedica are working on more efficient viral production systems but these will take time to optimise, validate and scale up.

Companies currently buy virus vectors in small batches (about 30 doses) from specialist manufacturers to use in their facilities. Each CAR-T cell type needs a different vector per target, although NKR CAR T-cells only need one type.

T-cell therapy production capacities are confidential, although Kite has a 5,000 dose facility. Processes to transform, grow and test the therapeutic product are standardised but still manual and very expensive due to the number of staff needed and the cost of the clean room facilities. Moving to a mass-produced product (highly-automated or allogeneic) will be essential for widespread use.

For larger mass markets allogeneic products may be needed. These are standardised cell lines manufactured in large batches and shipped to order or stored on site at major oncology centres. Allogeneic products have two hurdles.

- The first is the risk of graft vs host disease (GvHD). This is where transplanted donor cells mount an immune attack against the host. GvHD is well understood due to the experience of stem cell transplants and can be reduced by matching tissues – but this would complicate T-cell manufacturing. A more efficient solution is to remove or disable natural TCRs from the modified T-cells leaving only the chimeric TCR construct against the tumour.
- The second challenge is less understood and comprises host vs graft attack. This is where the donor immune system recognises the donated therapeutic T-cells as foreign and eliminates them: a transplant (graft) rejection. As current approaches are autologous, this is not a current problem unless the inserted CAR construct triggers an immune response. If donor rejection becomes an issue in allogeneic therapy design, it might be dealt with by partial tissue matching. An autologous T-cell therapy could be used as a fall back if an allogeneic one failed.

Overall, we would expect allogeneic to be the way forward for any mass market T-cell therapy as it could produce a standardised product and be immediately available at potentially much lower cost. As there are tenfold more solid tumours than blood cancers, improvements in process efficiency and price reductions will be essential.

### Technologies and patents in allogeneic

The two allogeneic protagonists are Celyad and Cellectis. Both are modifying T-cells to stop graft vs host disease. Cellectis has problems in clinical development; Celyad is planning trials.

Celyad uses TCR-inhibitory molecules (TIMs) currently in preclinical development; Celyad is planning an allogeneic study. The genes for TIMS are linked to the CAR gene construct used to transfect the cells. This means that NKR CAR T-cells should only bind the NKG2D ligands and cannot otherwise recognise host healthy tissues.

In November 2015, the US patent office granted US9,181,527 to Celyad. Claim 1 is broad and covers any TCR-deficient CAR T-cell to prevent graft-versus-host disease. No international filings were made so this patent only applies in the US. Claim 1 was challenged in 2016 but was upheld. Celyad holds other, later IP covering the TIM technology in detail.

Cellectis uses universal chimeric antigen receptors (UCART). These are produced after a gene editing process using transcription activator-like effectors nuclease technology (TALEN). This has also been patented. Cellectis has partnering deals with Servier in Europe and Pfizer in the US.

The allogeneic CAR-T therapy UCART123 started US trials for AML and refractory blastic plasmacytoid dendritic cell neoplasm, a sub-type of AML. However, the trials halted due to extensive side effects in two patients including one death after preconditioning and cell dosing. The cause for these side effects is not clear, but a new effect was Capillary Leak Syndrome, a poorly understood condition not seen in other precondition regimen. As UCART123 did not display GvHD in either patient, the major initial concern, the problems look to be product related rather than a general allogeneic issue.

## Investment scenarios

The T-cell therapy investment focus is currently on CAR-T in haematological cancers. This is logical given their relatively advanced development status, strong complete response data and accelerated approval by the FDA. Pricing by Novartis is as expected, about US$0.5m – albeit with a "money back" guarantee" if no response, an interesting gambit given that this pricing is unsustainable beyond highly restricted niche indications. However, standard CAR-T therapies address only smaller market segments, CD19 about 1%, of the overall cancer indication. Adding MM gives 3% coverage and if AML is also a market, the total coverage rises to 75,000 cases or 4.5% of US cancer incidence (Exhibit 4) and 30,000 deaths. As yet, overall survival gains are not known. There are also multiple companies and products that will or could have products in the area.

- One scenario could be that after an initial period when even limited demand runs ahead of restricted supply, manufacturing capability increases markedly and competition rises as a result. To expand the market and under strong pressure from payors and politicians, prices fall, leading, with high fixed costs, to a marginally profitable, overserved market.
- Alternatively, patient numbers may remain limited and prices high, creating a profitable but niche business. Expansion of the market is due to bispecific T-cell engagers (BiTEs) which are well suited to haematological cancers but with much lower costs.

Whatever the haematological outcome, the main investment prize will be in therapies that address solid tumours. It is not technically certain that standard CAR-T technology can treat solid tumours because of the antigen challenge and linked toxicity concerns.

A possible solid scenario is that the NKR CAR approach becomes the standard, with the introduction of an allogeneic format allowing rapid market expansion. Response rates will vary with cancer indication. Combinations with chemotherapy and checkpoint inhibitors are likely to be introduced. Customised autologous therapies may still be used for complex cases at much higher prices. TCRs prove effective in those patient segments that TCR products can address, perhaps up to half of each market after full development. However, if NKR CAR T-cell therapy shows similar efficacy to TCR, as is possible, NKR has the advantages of simpler administration and potentially manufacturing scale with lower costs. Given the scale of the solid tumour market need, prices will have to become more realistic and affordable, perhaps US$200k or lower.

An alternative scenario is that solid cancers remain intractable and that NKR and TCR give only marginal survival gains at high prices. This could still be a major pharmaceutical segment. Checkpoint inhibitors do not give most patients a cure or prolonged survival yet this is a very active development area and attractive market, at least for the market leader.

Finally, as Exhibit 6 shows, T-cell therapy is being developed by a range of new companies. Major pharma (Novartis excepted) has largely stayed clear of cellular products that are incompatible with its traditional small molecule and protein-based business models. There are collaborations running of course eg GSK with Adaptimmune, Pfizer and Servier with Cellectis, ONO with Celyad and various companies with Immunocore in BiTES including AstraZeneca. As with the original biotech companies, while some like Amgen remained independent, clinical success and established markets will trigger sector consolidation. This has started with Kit being acquired by Gilead. There are few leaders to acquire and Novartis may need to acquire another technology to break out of CD19. The Novartis licensing of allogenic technology from Celyad shows strategic intent to build a substantive market in this new and barely explored pharmaceutical space.

## Investment conclusion – seek new technologies

The solid cancer opportunity is tenfold greater than in haematological cancers with possibly 1.3m cancer patients a year (Exhibit 4). T-cell therapies could have major impact on many solid tumours if they are effective, if they can be made in quantity and if volume production makes them more affordable. Those approaches that meet these criteria will offer substantial investment returns – and massive benefits to patients and society.

Initially, this will not matter as the haematological opportunity at even half the current price is enormous. The haematological area though is not that large. CAR T-cells work very well in ALL and in DLBCL (which is about a quarter of non-Hodgkin lymphoma patients). That is 24,000 cases and 6,500 deaths a year in the US. Given the number of potential competitors and the high fixed costs of autologous cell manufacturing, this could be a very crowded market.

Multiple myeloma is addressable by CAR-T but there are other approaches in play as well. MM has 30,000 cases and 12,600 deaths a year so about the same incidence but twice the relapsed and refractory demands as the current B-cell CAR-T therapies. The MM market may initially be dominated by bluebird's bb2121, a BCMA CAR-T. The future market might be very varied as several approaches, including Celyad's NKR CAR T-cell therapy look promising.

AML becomes very intractable if a stem cell transplant is not possible. T-cell therapies or AML are still early and varied. This has 21,000 cases a year and 10,600 deaths.

Consequently, MM and AML offer greater potential than B-cell therapies. We should expect increasing development efforts and data in these cancer types.

As the haematological area begins to mature, which may be relatively fast over the next few years, investors need to look beyond the comfort zone of CD19 and BCMA CAR-T therapies. Eventually, the solid cancer area will become the new growth area and the current CD19 CAR-T leaders cannot easily diversify into solid tumours without investing in new technology and products. It is notable, for example, that Kite, Juno and Bellicum are all exploring TCR T-cell therapies.

The three technologies that might have a major future role in solid cancer therapy are NKR CAR and TCR T-cell therapies and allogeneic production. As the opportunities become better defined, investors should start to evaluate the next wave of major opportunities.

In Section 2, the underlying technologies and individual company approaches are discussed in more detail. This also provides more detail of the strengths and risks of each approach.

# Appendix 1: T-cell therapy terminology

Exhibit 10 gives a relatively non-scientific compilation of some terms used. This is advanced science even if this is over simplified.

**Exhibit 10: The components of the immune system needed for immune therapy**

| Name | Description |
|---|---|
| ALL | Acute lymphoid leukaemia – a fast growing cancer of the progenitor cells that make immune B and T cells. The cancer cells spill from the bone marrow into the blood. Patients become anaemic as few red blood cells made. Marked by CD19 antigens on their surfaces |
| Allogeneic | T-cells taken from one individual, treated and infused into a different person. This is in development for CAR-T cells and is the key to mass produced cheaper therapies. This is the best form of stem cell transplant as it eliminates any residual blood cancer cells in the host. |
| AML | Acute myeloid leukaemia - a fast growing cancer of the cells that make Natural killer and red blood cells amongst others. The immature cancer cells spill from the bone marrow into the blood. Patients become anaemic. Do not make CD19 so other antigens needed |
| Antibodies/B-cells/ Plasma cells | Antibodies (Ab) proteins that tightly bind antigens and are created by immature B-cells, another immune system cell type. They are produced by mature B-cells called plasma cells. Ab can have very tight binding to their target so can be made very specific. |
| Antigen/ ligand | Any protein or large molecule recognised by the immune system. Strictly, a ligand is any molecule that binds to a receptor so NKG2D (as a receptor) binds ligands. An antigen is a protein bound by an antibody or a peptide displayed on an MHC and recognised by a TCR. |
| Autologous T-cell | Cells extracted from a patient's blood, modified with CAR or TCR, cultured (expanded) and infused back into the same patient. |
| BiTE (Bi-specific T-cell engager) | A bi-specific antibody where one arm binds a cancer antigen. The other is a CD3 arm the binds and engages a CD8+ T-cell. Can be made more or less antibody like. The cancer antigen arm can be replaced by a TCR in one technology iteration. |
| Cancer or tumour antigen | An antigen seen mostly, ideally only, on the surface of a cancer cell that can be recognised by an antibody or immune cell. As cancer cells are human, it is hard to find antigens only shown by cancer cells and not by normal cells. However, cancers may make much more of some antigens than healthy tissues. Cancer cells also produce embryonic proteins (also called testis antigens) that are not made by adult cells. These fetal proteins are internal to the cells so can only be seen by TCRs. |
| Cancer vaccine | A peptide used to generate an immune response against a cancer. Many have been tried but they do not work consistently. |
| CAR-T therapy | A modified CD8+ T-cell with a Chimeric antigen receptor (CAR) added by insertion of synthetic genes to immune cells isolated from the patient's blood. Expensive customised therapy with high risk of side effects but can be very potent. |
| CD8+ T-cell | A powerful immune cell that if activated by its TCR binding to a specific peptide antigen shown in MHCI will kill tumour cells. Dangerous, potentially fatal, if out of control. Only needs to see 5-10 peptides to kill. |
| CD19 | Antigen found only on cancerous and healthy B-cells. It enables normal B-cells to develop new antibody types. |
| Checkpoint inhibitors (CPI) | Checkpoint proteins are natural protein signals that constrain the immune response. These help tolerance to cancer. Checkpoint inhibitors are antibody therapies that reduce tolerance enabling cancer cells in some patients to attack the tumour cells. |
| Chimeric antigen receptor (CAR) | An antibody-like artificial front end (usually scFv) outside the cell linked to a TCR signalling module inside the cell. If the front end binds its antigen target, the back end triggers the T-cell to attack. A CAR binds a specific cell surface antigen. |
| CRS Neurotoxicity | Cytokine release syndrome – uncontrolled release of inflammatory signals by over-excited therapeutic T-cells. Can be controlled by an antibody drug that binds IL-6. Can also be fatal. Immune reaction in brain to excessive inflammatory signals, linked to CRS. |
| Cytokines | Potent chemical protein messenger signals released by activated immune cells to trigger inflammation and stimulate other immune cells. |
| GvHD | Graft vs Host disease. This is when T-cells infused from another individual react against the host healthy tissues. These T-cells will then rapidly grow and attack organs etc. Can be fatal, Controlled by powerful immune supressing drugs and steroids. |
| MHCI (HLA) | A complicated and highly variable system for displaying short peptide antigens (fragments of internal cell proteins) on the cell surface. These are recognised by CD8+T-cells using a T-cell receptor (TCR). The advantage is its exquisite sensitivity: a single mutation in a specific MHC I type can be detected. Used in vivo to show that a cell is "self" and healthy, cells that fail the test are immediately killed. Cancer cells show fewer MHC I. MHC I is also called HLA and used for tissue typing in transplantation. |
| Modified TCR | A genetically engineered TCR recognising a specific peptide antigen on MHCI. It is implanted into a CD8+ T-cell. |
| Monoclonal | A single defined (engineered) antibody produced by a cloned cell line in large fermenters for use as therapeutics. Many research uses. |
| Multiple myeloma (MM) | Although this grows in the bone marrow, so is called myeloma and is around the skeleton (multiple), it is a lymphoid cancer of mature plasma cells derived from B-cells. Plasma cells do not show CD19. They do make BCMA (B-cell maturation antigen). |
| Natural killer cell (NK) | An immune cell type that detects and kills genetically damaged tissues. These use the natural killer group type 2D system (NKG2D) for detection. There are eight natural ligands. These cells do not attack "self" tissues normally. |
| NKR CAR | The NKG2D receptor with an added TCR signalling domain added and transplanted into a T-cell. This gives the recognition of an NK cell with the lethal power of a killer T-cell. |
| NHL/DLBCL | Non-Hodgkin's lymphoma. This is diverse set of white cell cancers similar to ALL. However, these grow in the lymph nodes around the body. DLBCL (diffuse large B-cell Lymphoma) – a subset of 25-30% of NHL cases showing the CD19 antigen. |
| scFv | Single chain variable fragment of an engineered antibody. Basically, a cut down binding arm of an antibody. Usually initially from mice but then adapted to be more "human" to stop an adverse immune reaction against therapy. Used in CAR-T therapies to target antigens. Can be coupled to others to make, for example, BiTEs. |
| TCR | T-cell receptor. A multi-part large protein on the surface of T-cells that binds MHC I with associated peptide. There are billions of possible TCRs. One TCR binds one peptide in one type of MHC1 very selectively. They can however, have multiple specificities. |
| Tolerance | When the patient's immune system recognises but does not attack a tumour despite "recognising" it. |
| Treg | Regulatory T-cells. Relatively small number of a CD4+ T-cell type that damps down any vigorous immune response. Unchecked immune responses can be fatal – Cytokine released syndrome is an example. |
| Tumour infiltrating Lymphocytes | Immune cells that recognise the tumour, but tolerate it. Therapeutically, these are extracted from the tumour of a patient, cultured and then reinfused in the usually vain hope that they will then attack the tumour. If activated by, eg checkpoint inhibitors, can be effective. |

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