BRYAN, GARNIER & CO

INDEPENDENT RESEARCH

# Cellectis

## Super Mario Car-T

9th March 2016

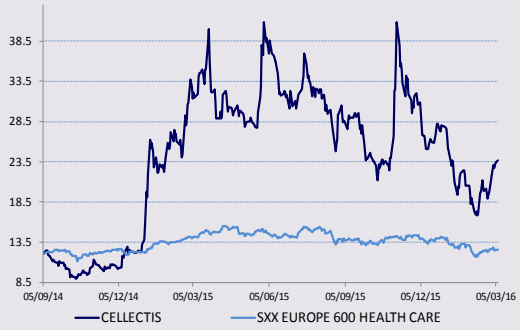
Healthcare

**Fair Value EUR37** (price EUR23.70) **BUY**

**Coverage initiated**

| | |
|---|---|
| Bloomberg | ALCLS FP |
| Reuters | ALCLS.PA |
| 12-month High / Low (EUR) | 40.9 / 16.9 |
| Market capitalisation (EURm) | 834 |
| Enterprise Value (BG estimates EURm) | 754 |
| Avg. 6m daily volume ('000 shares) | 216.9 |
| Free Float | 72.6% |
| 3y EPS CAGR | NM |
| Gearing (12/14) | -183% |
| Dividend yields (12/15e) | NM |

| YE December | 12/14 | 12/15e | 12/16e | 12/17e |
|---|---|---|---|---|
| Revenue (EURm) | 26.45 | 30.00 | 43.00 | 54.60 |
| EBIT(EURm) | -5.51 | -0.26 | 5.40 | 11.33 |
| Basic EPS (EUR) | -0.28 | 0.04 | 0.18 | 0.35 |
| Diluted EPS (EUR) | -0.28 | 0.04 | 0.18 | 0.35 |
| EV/Sales | 27.4x | 25.1x | 17.5x | 14.1x |
| EV/EBITDA | NS | NS | NS | 60.0x |
| EV/EBIT | NS | NS | NS | 67.9x |
| P/E | NS | NS | NS | 67.6x |
| ROCE | 13.7 | -7.1 | -51.9 | 71.3 |





**We are initiating coverage of Cellectis with a Buy recommendation and a FV of EUR37. The company is one of the rare developers of immunotherapies based on CAR T-cells that are genetically modified in order to better recognise and destroy cancer cells. The segment is in full boom and Cellectis is developing an approach that clearly stands out from the crowd since it is less costly and complex from a logistical perspective. Added to this, Cellectis has the ability to provide new modifications to these cells and has already signed two sizeable partnerships, leading us to believe that the group has what it takes to become a leader in this flourishing segment.**

- **A differentiating positioning.** The CAR T-cells developed by Cellectis have the specific feature of being allogeneic, meaning that 1) the modified immune cells are not extracted from and reinjected into a same patient (thereby providing the prospect of a standardised product), and 2) production could potentially be far easier and less costly than for rivals using autologous approaches. However, the difference does not stop there since Cellectis could also be capable of knocking out genes such as a PD-1, in order to strengthen its anti-tumour powers.
- **Heading for new validating deals.** Cellectis has already created two sizeable partnerships with Pfizer and Servier (combined milestone payments of USD3.8bn). However, we believe that other laboratories could show clear interest as soon as the first Phase 1 results implying the group's proprietary projects are published, and especially those for UCART38.
- **We are initiating coverage with a Buy recommendation and FV of EUR37.** The main de-risking factor would be the publication of Phase I results for UCART19 in treatment of acute lymphoblastic leukaemia, theoretically in 2017. However, more generally, we believe that the entire therapeutic class should benefit from the very first approval of a CAR T-cell in ALL treatment (CTL019 by Novartis). Last but not least, a more aggressive scenario would put our valuation at EUR120 per share.

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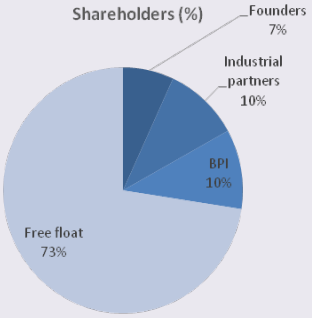


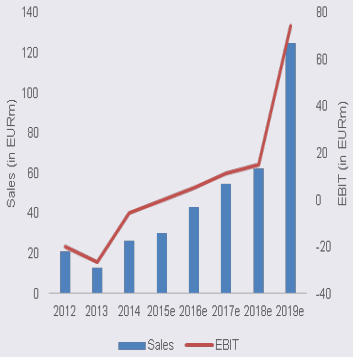


**Company description**

Cellectis is a French biotech company developing innovative cellular therapies to treat cancers

| Income Statement (EURk) | 2012 | 2013 | 2014 | 2015e | 2016e | 2017e | 2018e | 2019e |
|---|---|---|---|---|---|---|---|---|
| Revenues | 21.0 | 12.7 | 26.5 | 30.0 | 43.0 | 54.6 | 62.5 | 125 |
| *Change (%)* | *-%* | *-39.5%* | *108%* | *13.4%* | *43.3%* | *27.0%* | *14.5%* | *100.0%* |
| Adjusted EBITDA | (19.8) | (24.3) | (4.1) | 1.2 | 6.9 | 12.8 | 16.6 | 75.8 |
| EBIT | (19.8) | (26.5) | (5.5) | (0.26) | 5.4 | 11.3 | 15.1 | 74.3 |
| *Change (%)* | *-%* | *-34.0%* | *-79.2%* | *-95.2%* | *-%* | *110%* | *32.9%* | *394%* |
| Financial results | (1.3) | (0.32) | 1.9 | 1.5 | 1.0 | 1.0 | 1.0 | 1.0 |
| Pre-Tax profits | (21.1) | (26.8) | (3.7) | 1.2 | 6.4 | 12.3 | 16.1 | 75.3 |
| Exceptionals | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Tax | 1.2 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Profits from associates | NM | NM | NM | NM | NM | NM | NM | NM |
| Minority interests | NM | NM | NM | NM | NM | NM | NM | NM |
| Net profit | (22.3) | (56.4) | (6.5) | 1.2 | 6.4 | 12.3 | 16.1 | 75.3 |
| Restated net profit | (22.3) | (56.4) | (6.5) | 1.2 | 6.4 | 12.3 | 16.1 | 75.3 |
| *Change (%)* | *-%* | *-153%* | *-88.5%* | *-%* | *418%* | *92.7%* | *30.2%* | *369%* |
| **Cash Flow Statement (EURk)** | | | | | | | | |
| Operating cash flows | (14.7) | (21.5) | (5.1) | 2.7 | 7.9 | 13.8 | 17.6 | 76.8 |
| Change in working capital | 5.0 | (2.7) | (46.8) | 30.0 | 5.0 | 29.6 | 12.5 | 0.0 |
| Capex, net | 4.1 | 0.63 | 0.38 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| Financial investments, net | 0.0 | 0.17 | 1.5 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Dividends | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Other | NM | NM | NM | NM | NM | NM | NM | NM |
| Net debt | (17.5) | (3.5) | (109) | (79.9) | (81.3) | (64.0) | (67.6) | (143) |
| Free Cash flow | (23.9) | (19.5) | 41.3 | (28.8) | 1.4 | (17.3) | 3.6 | 75.3 |
| **Balance Sheet (EURk)** | | | | | | | | |
| Tangible fixed assets | 5.5 | 3.9 | 2.6 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Intangibles assets | 37.8 | 4.6 | 1.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Cash & equivalents | 21.8 | 7.6 | 112 | 83.6 | 85.0 | 67.7 | 71.3 | 147 |
| current assets | 38.9 | 19.9 | 132 | 103 | 105 | 87.4 | 90.9 | 166 |
| Other assets | 4.8 | 0.44 | 2.0 | 5.6 | 5.6 | 5.6 | 5.6 | 5.6 |
| Total assets | 87.0 | 28.9 | 138 | 109 | 110 | 93.0 | 96.5 | 172 |
| L & ST Debt | 4.3 | 4.1 | 3.7 | 3.7 | 3.7 | 3.7 | 3.7 | 3.7 |
| Others liabilities | 21.2 | 22.3 | 74.4 | 44.4 | 39.4 | 9.8 | (2.7) | (2.7) |
| Shareholders' funds | 61.5 | 2.5 | 59.5 | 60.8 | 67.2 | 79.5 | 95.5 | 171 |
| Total Liabilities | 87.0 | 28.9 | 138 | 109 | 110 | 93.0 | 96.5 | 172 |
| Capital employed | 44.8 | 1.9 | (47.3) | (17.3) | (12.3) | 17.3 | 29.8 | 29.8 |
| **Ratios** | | | | | | | | |
| Operating margin | (94.10) | (208) | (20.84) | (0.88) | 12.55 | 20.75 | 24.08 | 59.45 |
| Tax rate | (5.65) | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| Net margin | (106) | (443) | (24.52) | 4.12 | 14.88 | 22.58 | 25.68 | 60.25 |
| ROE (after tax) | (36.27) | (2,242) | (10.90) | 2.03 | 9.53 | 15.51 | 16.80 | 44.08 |
| ROCE (after tax) | (49.83) | (2,947) | 13.71 | (7.14) | (51.93) | 71.35 | 53.90 | 253 |
| Gearing | (28.48) | (139) | (183) | (131) | (121) | (80.54) | (70.73) | (83.63) |
| Pay out ratio | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| **Data per Share (EUR)** | | | | | | | | |
| EPS | (1.09) | (2.68) | (0.28) | 0.04 | 0.18 | 0.35 | 0.46 | 2.14 |
| Restated EPS | (1.09) | (2.68) | (0.28) | 0.04 | 0.18 | 0.35 | 0.46 | 2.14 |
| *% change* | *-%* | *-146%* | *-89.5%* | *-%* | *418%* | *92.7%* | *30.2%* | *369%* |
| BVPS | 3.00 | 0.12 | 2.58 | 1.73 | 1.91 | 2.26 | 2.72 | 4.86 |
| Operating cash flows | (0.72) | (1.02) | (0.22) | 0.08 | 0.22 | 0.39 | 0.50 | 2.18 |
| FCF | (1.17) | (0.92) | 1.79 | (0.82) | 0.04 | (0.49) | 0.10 | 2.14 |
| Net dividend | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |

*Source: Company Data; Bryan, Garnier & Co ests.*

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# 1. Investment Case

*Pourquoi investir maintenant?*

## Pourquoi s'intéresser au dossier maintenant :

Although the group had proven the feasibility of its technology, we were above all waiting for a first proof of concept in humans. This has now been achieved since an 11-month old girl suffering from acute lymphoblastic leukaemia (ALL) has gone into complete remission following treatment with UCART19. A second important point: Servier recently exercised its option on the same project, whereas this catalyst had not been expected before the publication of Phase I results. Against this backdrop, we think the recent fall has opened a window of opportunity on the stock.

*Attractif ou non?*

## Valorisation

Our FV works out to EUR37 per share based on a sum-of-the-parts (SOTP) valuation, where each part has been valued using a DCF calculation.

*Horizon d'investissement?*

## Catalyseurs

We see two sector catalysts for the next 12 months: 1) the very first marketing approval for a CAR-T (CTL019 by Novartis), as a sector catalyst, 2) the publication of new clinical data implying a competing CAR-T in solid tumours. In addition, we estimate that future feedback from the DSMB on the safety of UCART19 should provide qualitative factors likely to underpin the share price.

*Valeur ajoutée?*

## Différentiation face au consensus :

The fact that we cover Genmab and Innate Pharma has probably enabled us to better assess developments in the myeloma market, as well as the specific features of CD38 and CS1 antigens. We also believe that 1) the market underestimates the potential of UCART38 and 2) big pharmas like Sanofi should show clear interest in the drug (at least once the first Phase 1 data is communicated).

*Quels risques?*

## Risques

From our viewpoint, risks primarily concern the safety profile of Cellectis' approach. Although a young girl was treated with no notable problems in the context of a compassionate treatment, an accumulation of data over a wider number of patients from a clinical trial is clearly necessary.

Please see the section headed "Important information" on the back page of this report.

# 2. Pourquoi investir maintenant ?

For just under five years, approaches aimed at modulating and/or stimulating immune responses have been the focus of particular attention from scientists and the pharmaceuticals industry and in our report initiating coverage of Innate Pharma (Brace yourselves… AZN is coming (back)!), we focused especially on control point antibody inhibitors. While we believe these inhibitors are a genuine revolution for treatment of solid tumours, we would say that CAR T-cells are pretty much their equivalent for blood cancers (at least in the current state of play). Proof of this craze lies in the fact that several "small" companies developing approaches of this type have been floated on the stockmarket and already boast attractive capitalisations (Juno's is close to USD4-5bn despite the recent sell-off in the biotech sector).

Cellectis is one of the few pure players developing modified immunity cells. **While its projects are less advanced, we believe they are 1) well differentiated relative to other approaches currently being developed and 2) potential best-in-class drugs**. Whereas the majority of rivals are focusing on cells extracted from the patients themselves (autologous approaches), Cellectis is relying on its know-how in genome editing in order to develop allogeneic approaches, whereby the donor and the receiver are quite distinct. Less costly and less complicated to manufacture, and with potential add-ons, we think the therapies developed by this French biotech group have what it takes to create a leader in the sector.

The group's current portfolio includes four major projects and we would point out that Cellectis still owns the rights to three of these (UCART123, UCART38 and UCARCS1), whereas UCART19 is currently backed by two of the company's partners, Servier and Pfizer.

**Fig. 1: Cellectis - development pipeline**

| Program | Target | Potential Characteristics | Indications | Clinical stage | Alliance |
|---|---|---|---|---|---|
| UCART19 | CD19 | TCR + CD52 KO | Acute Lymphoblastic Leukemia | Phase I | Pfizer/Servier |
| UCART19 | CD19 | TCR + CD52 KO | Chronic Lymphocytic Leukemia | Phase I | Pfizer/Servier |
| UCART19 | CD19 | TCR + CD52 KO | Non-Hodgkin Lymphomas | TBA? | Pfizer/Servier |
| UCART22 | CD22 | TCR + CD52 KO | Acute Lymphoblastic Leukemia | Prec./Phase I | Wholly-owned |
| UCART22 | CD22 | TCR + CD52 KO | Chronic Lymphocytic Leukemia | TBA? | Wholly-owned |
| UCART22 | CD22 | TCR + CD52 KO | Non-Hodgkin Lymphomas | TBA? | Wholly-owned |
| UCART123 | CD123 | TCR + dCK KO | Acute Myeloid Leukemia | Prec./Phase I | Wholly-owned |
| UCART123 | CD123 | TCR + dCK KO | Blastic Plasmacytoid Dendritic Cell Neoplasm | Prec./Phase I | Wholly-owned |
| UCART38 | CD38 | TCR + CD38 + PD-1 KO | Multiple Myeloma | Prec./Phase I | Wholly-owned |
| UCART38 | CD38 | TCR + CD38 + PD-1 KO | Non-Hodgkin Lymphomas | Prec./Phase I | Wholly-owned |
| UCARTCS1 | CS1 | TCR KO, CS1 + PD-1 KO | Multiple Myeloma | Prec./Phase I | Wholly-owned |

*Source: Company Data; Bryan, Garnier & Co ests.*

**2016 should also be a transforming year for CAR-Ts** given that we expect marketing approval for the very first of these (CTL019 by Novartis) during H2 2016, and the potential publication of fresh clinical data involving CAR-Ts in solid tumours. Finally, we estimate that the **recent decline in the share price (-40/45% since November 2015) has opened an attractive window of opportunity** a speculative component (since Pfizer has a 10% stake in the capital, in addition to being a partner in

the development and marketing of several products) and various options in terms of business development.

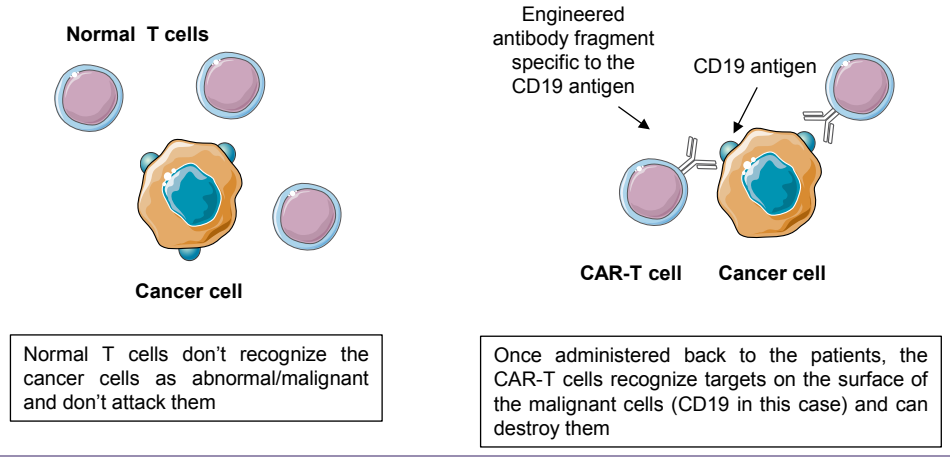
# 3. CAR-T or high-speed immuno-oncology

CAR-Ts, living drugs …

Before going into further details, we need to define what a CAR T-cell is. What we are talking about are **modified T-lymphocytes to which synthetic and antigen-specific receptors have been added** via the transfer of genetic material. In the current state of play, these powerful immunity soldiers have to be taken from the patient (in an autologous approach) before being modified and multiplied *ex vivo*. Once reinjected into this same person, they can then recognise and destroy cancer cells thanks to their new receptor.

**Several CAR-Ts targeting the CD19 antigen have shown incredible efficacy in various types of blood cancers** (acute lymphoblastic leukaemia probably being the indication in which complete response rates have been the most impressive). That said, the projects in development are not necessarily all of equivalent worth. A number of factors inherent in current CARs can affect performances such as an affinity of the receptor for the target and the co-stimulation domain etc. However, several companies are already working on these aspects and many others as well. In a sweeping generalisation, we could say that the first "Ford" Ts should leave the factories soon, while the future "Lamborghinis" are already being prepared. Bearing this in mind, it goes without saying that identifying the companies with the greatest innovation and adaption capacity is clearly important.

**Fig. 2: CAR T-cell action mechanism**




*Source: Bryan, Garnier & Co ests.*

## 3.1. Impressive results in blood cancers

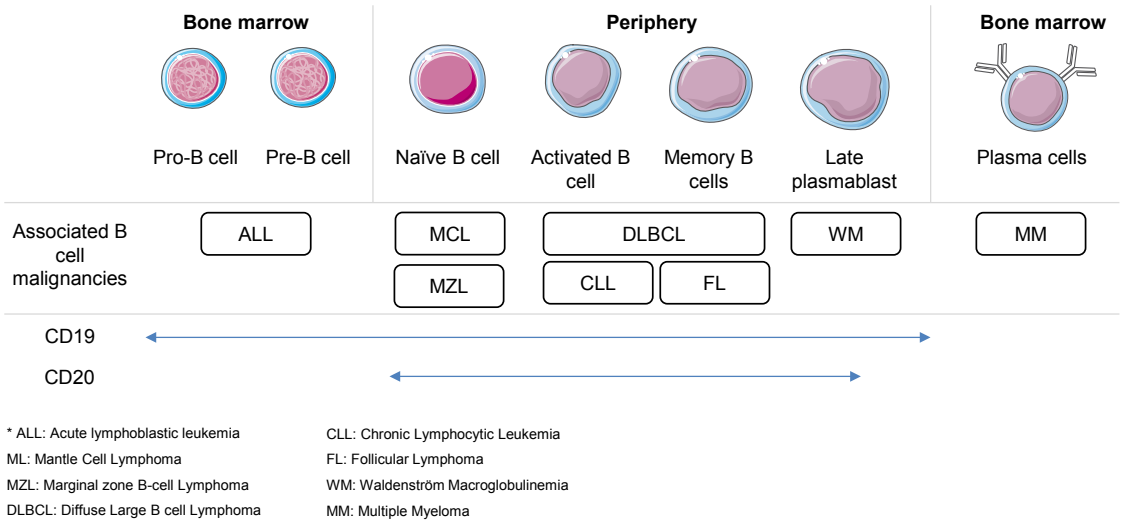
The first autologous CAR T-cells in development above all retained CD19 as the target for their synthetic receptor. This protein is very similar to CD20 (which was a corner-stone for the success of Roche and rituximab in hemato-oncology) in that 1) it was also over-expressed on the surface of cells form the B lineage, but 2) its spectrum is slightly wider in terms of evolution/maturing of B cells (see Fig. 3). In concrete terms, this implies a broader addressable market.

Complete response rate of more than 90% in ALL!

However, this is not why CAR T-cells are drawing so much attention. The reason is far more simple. Indeed, anti-tumour efficacy of this extent has never been seen before in patients heavily pre-treated and suffering from acute lymphoblastic leukaemia (ALL). Complete response rates have exceeded the

90% mark in monotherapy! In comparison, a bispecific CD3xCD19 such as blinatumomab only generated a CR rate of 43% in a similar setting (which could also be linked to its very limited half-life), whereas its toxicity profile is still far from optimal (Topp MS et al, Blood 2012).

**Fig. 3: Expression of CD19 and CD20 on the surface of line B cells**




*Source: Bryan, Garnier & Co ests. Adapted from Blanc et al, 2011*

**Fig. 4: Clinical results of CD19 CAR-T cells in ALL**

| Drug candidate | Clinical stage | Company | Antigen | Type of patients | Response rates |
|---|---|---|---|---|---|
| CTL019 | Phase II | Novartis | CD19 | Paediatric R/R ALL | 94% of Complete Remission |
| JCAR014 | Phase I | Juno | CD19 | Paediatric R/R ALL | 91% of Complete Remission |
| JCAR015 | Phase I | Juno | CD19 | Adult R/R ALL | 87% of Complete Remission |
| KTE-C19 | Phase I | Kite Pharma | CD19 | Paediatric & Adult R/R ALL | 70% of Complete Remission |

*Source: Companies Data*

NHL and CLL: less impressive response rates, but combos are being studied

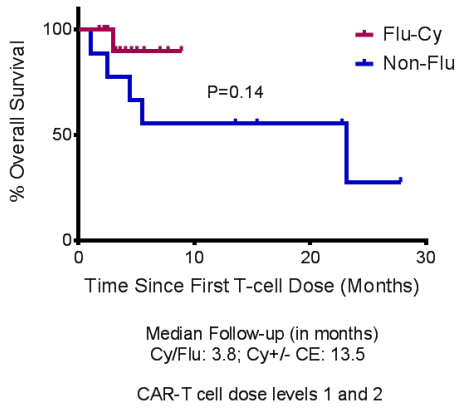
These same CAR T-cells have also generated full-response rates in indications such as chronic lymphoid leukaemia (CLL) or non-Hodgkin's lymphomas (NHL), although the rates were slightly less impressive than for ALL. Theoretically, this difference could stem from a far more challenging tumour micro-environment. For this reason in fact, combinations with immunotherapies (anti-PD-1 or PD-L1 to mention just these) or certain chemotherapies are currently being studied for these indications.

**Fig. 5: Clinical results of CD19 CAR-T cells in CLL and NHL**

| Company | Drug | Indications | Conditioning regimen | Efficacy data |
|---|---|---|---|---|
| Novartis | CTL019 | DLBCL | Fludarabine / Cyclophosphamide | 3-month ORR: 47% |
| Novartis | CTL019 | FL | Fludarabine / Cyclophosphamide | 3-month ORR: 73% |
| Kite Pharma | KTE-CD19 | NHL | Fludarabine / Cyclophosphamide | ORR: 78%, CR: 54% |
| Juno | JCAR014 (2*10^6/kg) | NHL | Fludarabine / Cyclophosphamide | ORR: 82%, CR: 64% |
| Juno | JCAR014 (2*10^6/kg) | NHL | Fludarabine / Cyclophosphamide | ORR: 100%, CR: 57% |

*Source: Companies Data*

**Fig. 6: NHL - Survival rates for JCAR014 with and without fludarabine**




*Source: Juno Therapeutics*

## 3.2. A last-line alternative?

While CAR T-cells are incredibly efficient, we nevertheless have the feeling that these approaches should remain last-line options. The fact that the first constructions are autologous makes the manufacturing process more complex and leads to prohibitive costs (around USD300,000-350,000 per patient!). However, we believe that their safety profile is probably what could limit market potential in the short and medium-terms.

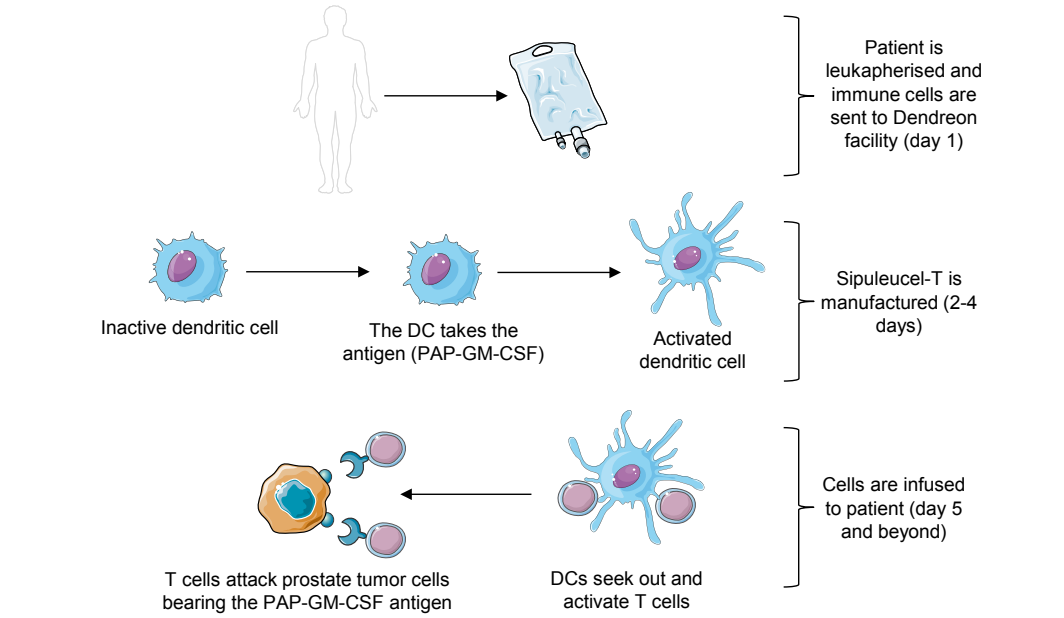
- **Logistical and cost issues that should not be underestimated**

Autologous approaches are costly and complex to produce, and the Dendreon story shows that this can impact the addressable market

A look in the rear-view mirror and especially at the Dendreon case, is fairly revealing in terms of the issues that autologous CAR T-cells can encounter. Dendreon was a small US biotech company whose main compound, Provenge (sipuleucel-T), was an autologous cell therapy dedicated to treatment of metastatic prostate cancer. The principle on paper was fairly attractive, namely to educate certain immunity soldiers (in this case dendritic cells) in order to better recognise cancer cells over-expressing the PAP-GM-CSF antigen. The results of a Phase III study notably showed an improvement in the median survival rate of 4.1 months (25.8 vs 21.7 months, HR: 0.775, p=0.032).

While the data bodes well, rival treatments (Zytiga and Xtandi to name just two) were admittedly just as good. In addition, in view of 1) all the logistical and biological constraints necessary for its production (see Fig. 7) and 2) the fact that a small company needs to face far more imposing rivals boasting far more user-friendly alternatives (oral administration), everything was set up for the product to be a commercial failure (around USD300m in sales whereas the consensus was expecting a blockbuster worth several billion).

**Fig. 7: Provenge (sipuleucel-T) – Preparation and action mechanism**




*Source: Dendreon; Bryan, Garnier & Co ests.*

However, does this mean that current CAR-T's will obviously be a commercial failure? Not necessarily. If we continue in our parallel with Provenge, we would say that these new approaches 1) now have rivals in terms of efficacy and that 2) several big pharmas and biotechs are investing huge sums in order to improve the design of these "living drugs" with Cellectis working on allogeneic options for example. In reality, the issue lies far more in the toxicity profiles of these new approaches.

- **The other side of the coin: significant toxicity to manage**

Toxicity of CAR-T limits its move up the treatment scale

Before going any further, we think it is useful to detail the immune response triggered by CAR T-cells. As mentioned previously, these are T lymphocytes to which receptors have been added by genetic engineering, thereby enabling the cells to directly detect cancer cells carrying a very precise antigen. In other words, the most powerful soldiers in our immune system can be activated and mobilised via a unique mechanism, whereas a whole cycle including a large number of other cells and chemical messengers are normally involved. Indeed, it is in overriding this extremely complex mechanism that CAR T-cells manage to obtain the powerful anti-tumour capacity that characterises them. However, this also explains their toxicity profile.

Once activated, these numerous cells indeed generate various immune response mediators (IFN-γ, IL-6, TNF-α, etc.). While they help accentuate the anti-cancer action by recruiting other lymphocyte populations, they also generally go hand-in-hand with significant inflammation. In extreme cases, a number of patients can suffer life-threatening conditions such as cytokine release syndrome (CRS) the impact of which is far from harmless (20-30% of cases in trials involving patients suffering from ALL), and which are capable of generating considerable additional costs (since their management involves administration of anti-IL-6 such as tocilizumab).

Another issue raised during clinical trials is tumour lysis syndrome, a metabolic complication caused by the massive and brutal liberation of cell waste. Here again, this is a side effect associated with the rapid tumour destruction enabled by CAR T-cells.

With this in mind, we struggle to see how cell therapies can impose themselves as first-line alternatives, especially since certain therapies marketed or being developed are actually fairly efficient, while offering acceptable toxicity levels (such as regimes based on asparaginase and cytarabine for ALL, and ibrutinib/venetoclax in CLL).

## 3.3. Solid tumours: an addressable market more for the medium term

Extension to the solid tumours market is challenging with current CAR-T constructions

As we write this report, CAR T-cells currently being developed and especially the most advanced of these, are above all destined for blood cancers. While solid tumours are not out of reach, the challenges they face are extremely complicated and for this reason, we favour a degree of caution pending new CAR-T designs and more in-depth data.

- **What antigens to choose?**

First hurdle to get over: choosing an antigen sufficiently specific to cancer tissues

The main protein-targets chosen (CD19, CD22) for construction of the receptor are above all overexpressed by blood cancers, and ultimately fairly little by solid tumours. Quite the contrary, otherwise there would not have been as many developments such as cancer vaccines! However, experience shows that they are not always very specific for tumour cells, such that an attack on healthy tissues by CAR-T is a risk that should not be underestimated.

**Fig. 8: CAR-T cells - Potential target antigens in solid tumours**

| Antigen | Companies/Centers | Potential indications |
|---|---|---|
| EGFRvIII | Novartis, Juno and Kite | Glioblastoma, glioma |
| Mesothelin | Novartis | Mesothelioma, Pancreas, Ovarian |
| NKG2D ligands | Celyad | Ovarian, Lung, Melanoma, Prostate |
| MUC16 | Juno | Ovarian |
| NY-ESO-1 | Adaptimmune | Multiple Myeloma |
| HER2 | Baylor | Breast, Glioblastoma |
| ROR-1 | Juno | Non disclosed |
| L1CAM | Juno | Neuroblastoma |
| MAGE A3 | Kite Pharma | NSCLC, SCC, Bladder, Melanoma |

*Source: Company Data; Bryan, Garnier & Co ests.*

Several interesting antigens are currently being explored. For example, EGFRvIII and mesothelin are among those retained by laboratories such as Novartis and Juno. For the moment, the first clinical data has shown no real toxicity issues, although the response obtained so far are still not very impressive (in the case of CAR-T-meso, patients benefited at best from a stabilisation in their disease with a single but low dose). We will see whether future data will be more encouraging with the adoption of different protocols (chemotherapy conditioning regime, higher doses, etc.).

Combinations: a way of addressing a challenging tumour micro-environment

- **Combinations: part of the solution**

Beyond the simple question of the target, the **modified T cells must face several obstacles within the tumour micro-environment,** especially in solid tumours: immunosuppressive cytokines (IL-10, TGF-β), regulating cells (Tregs), presence of inhibitor co-receptors (PD-1, CTLA-4, LAG-3, TIM-3), etc.

Here again, combinations with other immunotherapies could be a good way of getting round the problem. The first clinical data collected from CAR-Ts targeting HER2 (Morales-Kastresana et al, 2013) showed in particular that 1) combination with an anti-PD-1 seems to result in far deeper responses than each monotherapy taken separately and, 2) intriguingly, the number of immunosuppressive cells (such as MDSCs) were significantly reduced.

## Heading for new CAR-T designs

Tomorrow's Lamborghinis already in development

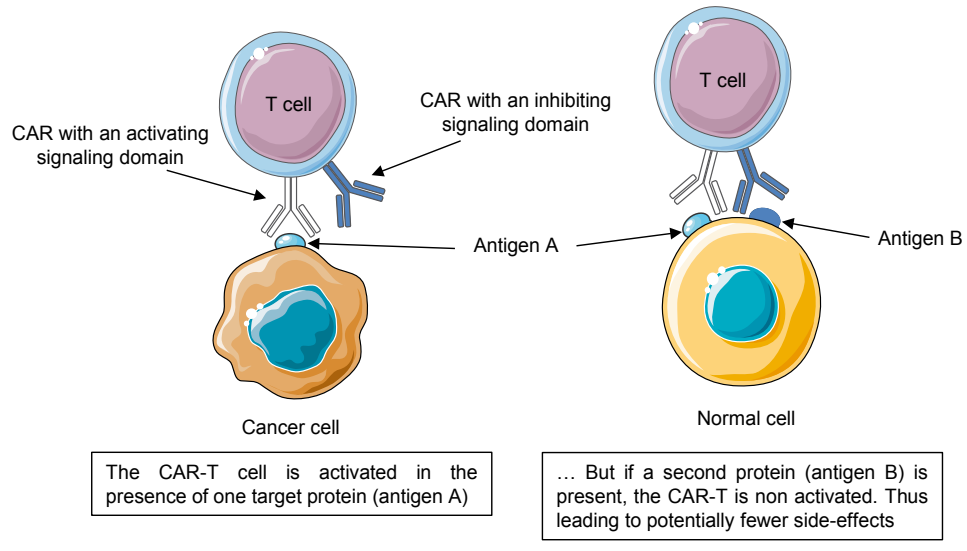
Construction of a CAR-T is not set in stone and we would also note that we are already at a third-generation stage. As such, it is not surprising that reflections are underway for all forthcoming lines, with the idea being to improve the safety and efficacy profile (and consequently, to facilitate extension in the application scope to solid tumours). Among these different strategies, three look fairly attractive:

- **Adding a second receptor in order to target two antigens.** It would also seem that this strategy could integrate a double recognition that would be necessary to activate or de-activate the modified T lymphocyte.

- **Adding another co-stimulation domain** (MyD88/CD40 for example?). The vast majority of CAR T-cells developed are indeed based on CD28 and 4-1BB, the former apparently resulting in a faster proliferation of cells whereas the latter apparently helps improve the persistence of cells over the long term (although this is all still very hypothetical). Adding a new domain could potentially help go further in these various aspects.

- **Enabling T lymphocytes to produce other types of chemical messengers.** These powerful immunity soldiers can directly attack tumour cells (especially CD8+), although it is important to note that their destructive power also involves generating pro-inflammatory chemical messengers and is only limited to a few of these. In fact the idea would be to enable modified T cells to produce other types of cytokines (IL-12 for example) in order to strengthen the immune response.

**Fig. 9: Example of a CAR-T bispecific construction**




*Source: Adapted from Juno Therapeutics, Bryan, Garnier & Co. ests*

## 3.4. A look at the competition

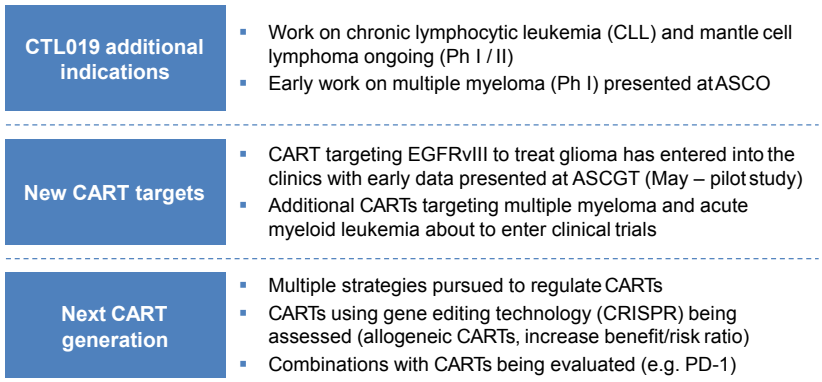
### Novartis: a cautious first-mover

CTL019: a first approval as of 2016, but with limited marketing prospects

Novartis stands out on radar screens fairly easily since its CAR-T anti-CD19 (known-as CTL019) could be the first to be approved in ALL treatment, and it goes without saying that this would have a positive impact on the entire therapeutic class. That said, note that the company remains fairly cautious as to the outlook for CTL019 for all of the reasons we mentioned previously.

Thereafter, we are set to focus more on the procedure it intends to use to produce allogeneic CAR-Ts (deletion of TCRα gene or a cousin gene, insertion of a gene with a negative impact on the formation of TCR?). In addition, we understand that multiple myeloma is clearly one of the markets it would like to address. Since CD19 is not the most appropriate target, we believe that the Swiss pharma group should develop new receptors with an affinity for other targets (CD38 or CS1?).

**Fig. 10: Novartis – Development strategy in CAR-T**




*Source: Novartis, Meet the management (June 2015)*

### Juno Therapeutics or the carpet-bombing strategy

The group's three main projects (JCAR015, JCAR014, JCAR017) target the same antigen (CD19), but each of these presents 1) small variations in terms of their construction (virus used for transduction, co-stimulation domain chosen) and 2) a pre-defined ratio of T lymphocytes CD8+/CD4+ (1:1 in the case of JCAR014), the basic premise being that the safety profile could be improved (although data available so far does not seem to confirm this yet).

Juno's strength lies in its various partnerships and the cash provided by Celgene

Juno Therapeutics' technological edge is not really palpable if we limit ourselves to published clinical data in various blood cancer types. In truth, we would even say that it is not very different to its main rivals (Kite Pharma, Bellicum Bluebird and Novartis). From our viewpoint, Juno's leadership lies more in the agreement signed with big pharmas and biotechs such as Celgene, as well as the accompanying financial terms (upfront payment of USD1bn) and the fact that this deal indirectly provides the possibility of testing its various candidates with other approaches such as AstraZeneca's durvalumab (anti-PD-L1).

Strengthened by this financial clout, the biotech company can therefore launch a number of differentiating developments at the same time (albeit still very early stage) - "armoured CARs", "bispecific CARs" with the end-point theoretically being to facilitate the bridge towards solid

tumours. It is also likely that projects are still secret today and we would not be surprised if an allogeneic approach were to be developed in partnership with Editas Medicine in coming months (why would Celgene have invested so much in the company otherwise?).

**Fig. 11: Juno Therapeutics – development pipeline**

| Program | Antigen | Indications |
|---|---|---|
| JCAR015 | CD19 | Adult ALL (Phase II)<br>Adult NHL (Phase I) |
| JCAR017 | CD19 | Paediatric ALL (Phase I/II)<br>Adult NHL (Phase I/II) |
| JCAR014 | CD19 | Adult B cell malignancies (Phase I/II)<br>Exploratory pathways (cell population, immune modulation, others) (Phase I) |
| JCAR021 | CD19 | Adult B cell malignancies (Phase I) |
| "Armored CAR" | CD19 | Adult B cell malignancies (Phase I/II) |
| JCAR in combination with anti-PD-L1 | CD19 | Adult NHL (Phase I) |
| JCAR018 | CD22 | Paediatric ALL/NHL (Phase I) |
| JTCR016 | WT-1 | Adult AML (Phase I/II)<br>Adult NSCLC (Phase I) |
| JCAR023 | L1CAM | Paediatric neuroblastoma (Phase I) |
| JCAR020 ("Armored") | MUC16 & IL12 | Ovarian cancer (Phase I) |
| CAR | ROR-1 | Solid tumours (Phase I) |

*Source: Juno Therapeutics, JPMorgan Healthcare Conference (January 2016)*

**Fig. 12: Juno Therapeutics – Partnership agreements and acquisitions**

| Partner | Purpose |
|---|---|
| Celgene | Celgene gained options to commercialise Juno programmes outside North America and co-promote certain programmes globally<br>On the other hand, Juno got an option to co-develop and co-promote selected Celgene programmes |
| AstraZeneca | The two companies agreed to conduct a trial evaluating durvalumab (anti-PD-L1) with a CD19-directed CAR-T in NHL, and potentially other indications |
| Editas Medicine | The two companies will pursue three research programmes together utilising Editas' genome editing technologies, including CRISPR/Cas9 with Juno's CAR and TCR technologies<br>We assume the future projects will include allogeneic approaches |
| Fate Therapeutics | Identifying and utilising small molecules to modulate Juno's genetically-engineered T cell product candidates to improve their therapeutic potential for cancer patients |
| Opus Bio | Juno entered into an agreement to obtain a license from Opus Bio for a CAR-T product candidate targeting CD22, whic<br>was incidentally developed by the NCI under cooperative R&D with Opus<br>A Phase I was launched to evaluate the compound in paediatric and young adults with ALL or NHL and both CD19+ and CD19- |
| Stage cell therapeutics | Stage develops a technology platform based on fully reversible reagents that enable an advanced isolation and expansion of T cells during the manufacturing process<br>Juno said it will invest in commercially scaling these technologies for incorporation into next-gen CAR-T and TCR product candidates |
| X Body Biosciences | Juno acquired the company to incorporate its platform into its process for creating CAR-T constructs, using it to generate to generate new binding domains with reduced immunogenicity, hence leading to improved CAR-T cell in vivo persistence |

*Source: Company Data; Bryan, Garnier & Co ests.*

### Kite Pharma: a greater focus on TCRs?

Like Juno, Kite Pharma currently benefits from the backing of a major pharma group (Amgen in this case) for the development of various autologous CAR-Ts (upfront payment of USD60m, USD525m in potential additional payments per project selected). Very synthetically, we would say that 1) the group's lead candidate, KTE-CD19, does not really stand out from other CAR-T anti-CD19 (beyond the fact that non-Hodgkin's lymphomas should be the very first indication for which marketing approval should be obtained), 2) Kite's differentiation ability lies above all in the other projects developed and the accent that was placed on TCRs as well as solid tumours (while bearing in mind that the application scope could be larger than for CARs).

**Fig. 13: CAR-T vs TCR**

| | CAR | TCR |
|---|---|---|
| Antigens targeted | Surface only | Surface or intracellular |
| Requirement for antigen processing and presentation | No | Yes |
| Generation of new specificities | Relatively easy, dependent on the availability of antibodies | More challenging, depends on the identification of relevant tumour-specific TCR |
| Signal potency | High and can be further enhanced with co-stimulatory domains | Relates to the affinity of the native TCR complex but can enhanced by mutagenesis |
| Off-target effects | Can target normal tissues with low levels of expression, there are few surface markers with truly tumour restricted expression | Can potentially target normal tissues with low levels of expression even without degeneration of specificity |

*Source: Company Data; Bryan, Garnier & Co ests.*

**Fig. 14: Kite Pharma – development pipeline**

| Program | Antigen | Targeted indication | Clinical stage |
|---|---|---|---|
| **CAR-T** | | | |
| KTE-C19 | CD19 | Diffuse Large B cell Lymphoma, Transformed Follicular Lymphoma, PMBCL | Phase II |
| KTE-C19 | CD19 | Mantle Cell Lymphoma | Phase II |
| KTE-C19 | CD19 | Adult Acute Lymphoblastic Leukaemia | Phase I |
| KTE-C19 | CD19 | Paediatric Acute Lymphoblastic Leukaemia | Phase I |
| KTE-C19 | CD19 | Chronic Lymphocytic Leukaemia | Pre-IND |
| Unnamed | EGFRvIII | Glioblastoma | Phase I |
| Unnamed | Unknown | Solid tumours and Heme malignancies (Amgen collaboration) | Pre-IND |
| **TCR** | | | |
| Unnamed | NY-ESO-1 | Solid tumours | Phase II |
| Unnamed | MAGE A3 | Solid tumours | Phase I |
| Unnamed | MAGE A3/A6 | Solid tumours | Phase I |
| Unnamed | HPV-16 E6 | Cervical and head & neck cancer | Phase I |
| Unnamed | HPV-16 E7 | Cervical and head & neck cancer | Pre-IND |
| Unnamed | SSX2 | Solid tumours | Pre-IND |
| Unnamed | KRAS | KRAS mutation tumours | Pre-IND |

*Source: Kite Pharma Presentation (Jan 2016)*

# 4. Cellectis: a future leader in the making

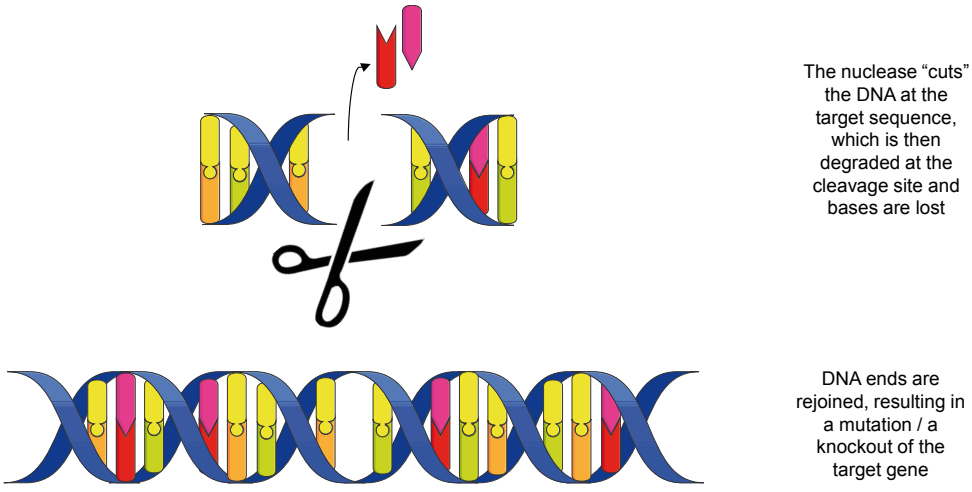
The competitive backdrop has widened considerably in recent months. For the moment, Juno looks well positioned to stand out massively from other major players in the sector. In these conditions, it remains to be seen whether there is any space left for smaller companies. We would say there is, but on condition that they provide genuine innovations! In this respect, Cellectis has a very attractive hand, boasting: 1) the possibility of having an allogeneic therapy, lighter on the financial and logistics fronts, and 2) the transfer of other functionalities to these modified immune cells, with PD-1 gene knock-out being an alternative among others.

The fact that the group has Pfizer as its main partner in development and marketing of various projects is also an important point in our investment case. The US laboratory is one of the serious challengers in the immuno-oncology field and for the moment, the CAR-Ts developed by Cellectis seem to be the most differentiating projects in the big pharma's portfolio. As such, we believe that the various UCARTs developed could rapidly become priority projects.

## 4.1. Heading for allogeneic CAR-Ts, cheaper and even more..

Cellectis' current CAR-T platform was created from its ability to develop/generate genome modification tools, meganucleases, which are proteins capable of cutting very specific parts of double strand DNA in living cells (which is why they are sometimes referred to as gene surgeons).

**Fig. 15: TALEN or smart DNA cutting**




*Source: Cellectis; Bryan, Garnier & Co ests.*

Development of allogeneic CAR-Ts involves elimination of the TCR

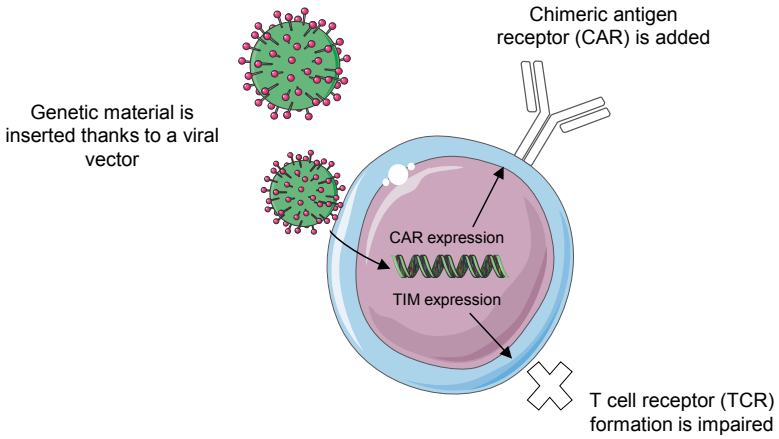
So how is an allogeneic formed thereafter? We now know that the main risk lies in use of this type of approach in the emergence of a phenomenon known as graft-versus-host disease (GVHD) whereby 1) the injected cells start attacking those of the receiver after identifying them as foreign (this can obviously cause serious damage and a high level of mortality), 2) the recognition involves receptors located on the surface of the T cells and known as TCRs. **In order to get round this problem, Cellectis de-activates the TCRα gene**, which is a central element of the TCR and hence in the

development of a GVHD-style reaction. If we go further into the technical details, our comments would be the following:

- Other companies have also assumed that neutralisation of TCR enables a huge reduction in the risk of GVHD. And in the case of Celyad, we understand that this involves the insertion of a gene inhibitor (TIM), which should prevent the TCR from forming or which prevents it from functioning correctly.

- Theoretically, withdrawing a receptor such as TCR should not be an issue in the case of CAR-Ts. since recognition of cancer cells and activation of the T cell goes via the synthetic receptor.

**Fig. 16: Manufacturing process for Celyad's allogeneic CAR-Ts**




*Source: Celyad, Bryan, Garnier & Co. ests*

- **A first important step: towards standardised products that are less complicated to produce**

UCART: cheaper projects that are less complex to produce

The first advantage, and the most obvious one, concerns logistics, namely rapidly obtaining a fairly standardised product that is easily available (relative to autologous CAR-Ts in any case). Thanks to this simplification in the production chain, the other consequence lies in costs. Without even mentioning economies of scale, we understand that the cost price for each vial currently stands at EUR15,000. And once the process is optimised (automation, electroporation over a larger number of lymphocytes etc.), the company hopes to reduce this figure to almost EUR5,000!

On this premise, Cellectis would clearly have plenty of room to manoeuvre in fixing prices of its treatment (whereas autologous therapies are not easy to get below USD300,000 per patient without denting margins).

In short, there are plenty of advantages. However, a number of points still have no clear answers and this should be borne in mind. Should doses and the number of administrations be increased? And is this possible without overly affecting the security profile? The company nevertheless seems aware of the challenges inherent in the development of allogeneic therapies and this is also why other editions are being envisaged today.

**Fig. 17: Allogeneic vs autologous - Advantages and disadvantages**

| | Autologous | Allogeneic |
|---|---|---|
| Cost of manufacturing | High (hence the very high treatment price) | USD5,000-15,000 per vial (Cellectis estimate) |
| Availability | Few days due to the manufacturing | Immediate |
| | Cell supply potentially limited (lymphopenia) | High supply, due to the number of donors |
| Editing | Limited by cell supply and inefficiencies | Much less limited, the only hindrance being the risk of mis-translocation |
| GVHD risk | No | Yes (but TCR editing should reduce it) |

*Source: Company Data; Bryan, Garnier & Co ests.*

- **Going further than simple allogeneicity!**

Add-ons in order to improve the safety and efficacy profile of CAR-Ts

The fact that the group is developing an allogeneic approach that is potentially less costly, is already a significant differentiation factor. However, we have the impression that the market underestimates the group's ability to modify and add other key properties of T lymphocytes thanks to its DNA cutting technology. Among the various possibilities that we were able to discuss with management, three of these seem to be of particular interest:

- **Inserting a gene enabling a switch-on**. The principle is relatively simple: integrating an activation mechanism thanks to a small molecule, which could be very useful for patients suffering from too many side effects (cytokine release syndrome, on-target/off-tumour effect etc.). Bellicum is developing autologous CAR-Ts with a self-destruction ability. Here again, this would help better control eventual side effects, although this also implies total eradication of the modified cells, and hence a premature end to the treatment.

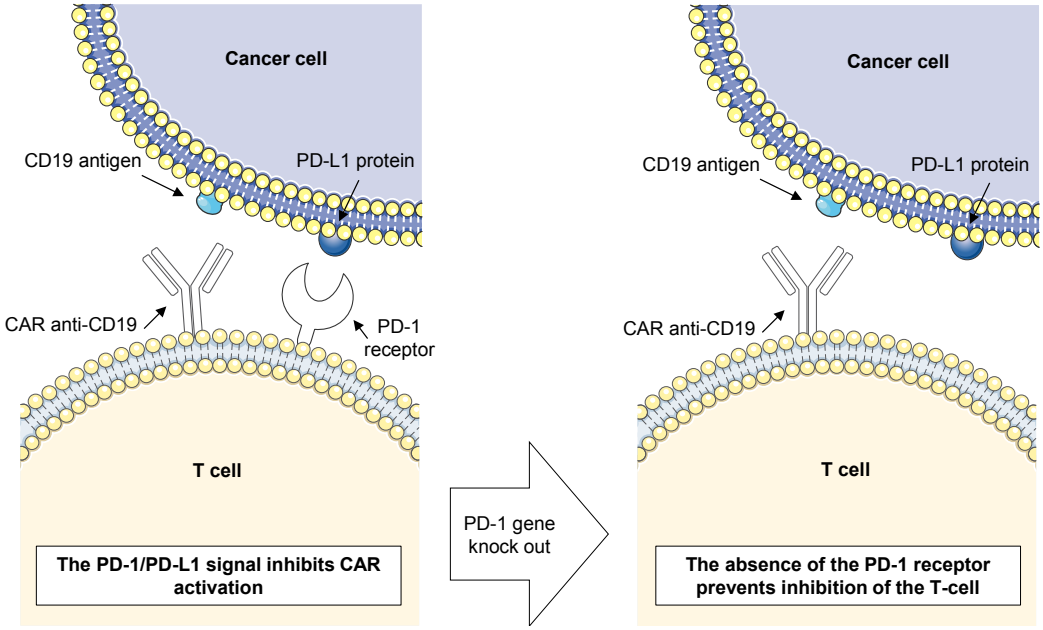
- **Eliminating a gene and creating resistance to eventual simultaneous treatments.** For example, by neutralising the formation of CD52, Cellectis can produce cells resistant to therapeutic antibodies targeting this protein (e.g. alemtuzumab), and therefore capable of being administered at the same time as these. On the one hand, it would appear that the inactivation of kinase deoxycytidine (dCK) could help increase resistance of CAR-Ts to lymphodepleting chemotherapies such as fludarabine, cytarabine and clofarabine.

- **Focus on PD-1 gene knock-out**

Among the various strategies that the company intends to explore, that of knocking out the PD-1 gene looks particularly attractive. We have stated several times in this report that combinations of CAR-Ts and anti-PD-1/PD-L1s are among the developments being made by big pharma groups and small pre-clinical trials show that this option could effectively result in greater tumour regression. **The interaction between PD-1 and PD-L1 proteins is currently viewed as a major escape strategy for tumours to immune response** with clinical data involving antibodies preventing this connection seeming to back this theory in any case. And after several years of development, a certain amount of information has transpired: 1) the more PD-L1 is expressed, the more the therapies are efficient, 2) its expression is fairly volatile and can be accentuated by intrinsic factors such as IFN-gamma (chemical messengers also widely generated by lymphocytes, at least once they are activated).

**PD-1 knock-out is of no real interest in a cancer case such as ALL. However, it could be essential for indications such as myeloma and non-Hodgkin's lymphomas** where the said protein is expressed very strongly (see Fig. 19). We will see what clinical data is obtained with the approaches developed by Cellectis, but one thing is certain: given the low cost caused by adding a knock-out gene, the company could benefit from a clear price-advantage that would facilitate its combination with other therapy types (which is unlikely to be a luxury in the current context).

**Fig. 18: Interest of PD-1 knock out**




*Source: Cellectis; Bryan, Garnier & Co ests.*

**Fig. 19: Expression of PD-L1 depending on tumour type**

| Cancer type | PD-L1 expression | Tumour-infiltrated immune cells? |
|---|---|---|
| Melanoma | 40-100% | Yes |
| Non-small cell lung cancer | 35-95% | Yes |
| Nasopharyngeal | 68-100% | Yes |
| Glioblastoma | 100% | Yes |
| Colon adenocarcinoma | 53% | Yes |
| Hepatocellular carcinoma | 45-93% | Yes |
| Urothelial/bladder | 28-100% | Yes |
| Multiple myeloma | 93% | Yes |
| Ovarian | 33-80% | Yes |
| Oesophageal | 42% | Yes |
| Pancreatic | 39% | Yes |
| Renal cell carcinoma | 15-24% | Yes |
| Breast | 31-34% | Yes |
| Lymphomas | 17-94% | Yes |
| Leukaemias | 11-42% | No |

*Source: Chen DS et al, 2012*

■ **What other approaches in gene editing?**

Cellectis is admittedly not the only company developing allogeneic CAR T-cells. Novartis and Celyad have already announced that they are working on this type of project and we would not be surprised if Juno also joins the race. However, this does not necessarily mean that Cellectis' approach is invalid. The small biotech company is today still the most advanced in the search for the new grail of CAR T-cells, and we believe that all of the know-how behind its platform makes it more precise and hence safer.

At present, two other gene editing methods co-habit with the TALEN platform although we would say that the CRISPR/Cas9 method is the one that has caught our eye most (and not only because it is the one that Juno and Novartis seem to have chosen). In both cases, the editing involves the use of endonucleases (or molecular scissors) in order to change a precise sequence of DNA (inactivation, correction and insertion). CRISPR/Cas9 is clearly a hugely interesting technique given its rapidity/productivity and its limited cost. However, on another level, we understand that Cellectis could 1) induce far fewer off-target effects (which is far from insignificant given that these are sometimes difficult to find) and complication risks, and 2) could be more sensitive when it comes to DNA breaking (thus leading to a much better yield).

**Fig. 20: Comparison of various gene editing platforms**

| | TALEN | CRISPR/Cas9 | ZNF |
|---|---|---|---|
| Companies | Cellectis (Pfizer/Servier) | Editas (Juno), Instella (Novartis) | Ziopharm |
| Specificity | Limited number of mismatches tolerated | Multiple mismatches tolerated | Limited number of mismatches tolerated |
| Methylation sensitive | Sensitive | Not sensitive | Unknown |
| Off-target effects | Low | Moderate/High | High |
| Ease of engineering | Easy | Easy | Difficult |

*Source: Company Data; Bryan, Garnier & Co ests.*

## 4.2. First validating and structuring deals

Already two partners and overall payment potential of USD3.9bn

**In June 2014, Cellectis announced the signing of a partnership agreement with Pfizer.** According to the terms of the contract, the big pharma will have exclusive rights to the development and future marketing of the CAR-Ts directed against 15 targets that it would have chosen. However, the agreement also plans for a total of 12 targets selected by Cellectis. The two companies are to undertake preclinical research works for four of these and Pfizer has a right of refusal for these. Cellectis is to work independently on eight others and will also be responsible for their development as well as their eventual marketing.

Note that Pfizer has paid USD80m upfront as well as funds of an undisclosed amount to cover R&D costs for the 15 projects that it has chosen and four of the 12 targets chosen by Cellectis that are the object of joint works. Thereafter, Cellectis is likely to receive additional payments that could total USD185m per product, as clinical, regulatory and commercial milestones are crossed. A last important point to underscore: **back then, the US laboratory pledged to take a stake of around 10% in the capital via a reserved rights issue with cancellation of preferential subscription rights.**

**Fig. 21: Main financial elements of deals with Servier and Pfizer**

| Partner | Other comments | Financial terms |
|---|---|---|
| Servier | - Servier will develop and commercialise up to 6 targets including CD19, the others are rather solid tumours-oriented | - Upfront payment: USD10m (USD38m for UCART19)<br>- Milestone payments: USD140m per Servier product (USD300m for UCART19)<br>- Royalties: tiered, high-single digit |
| Pfizer | - Pfizer will develop and commercialise up to 15 projects/targets<br>- The agreement provides for a total of 12 other targets selected by Cellectis | - Upfront payment: USD80m<br>- Milestone payments: USD185m per Pfizer product<br>- Royalties: tiered, high-single digit |

*Source: Company Data; Bryan, Garnier & Co ests.*

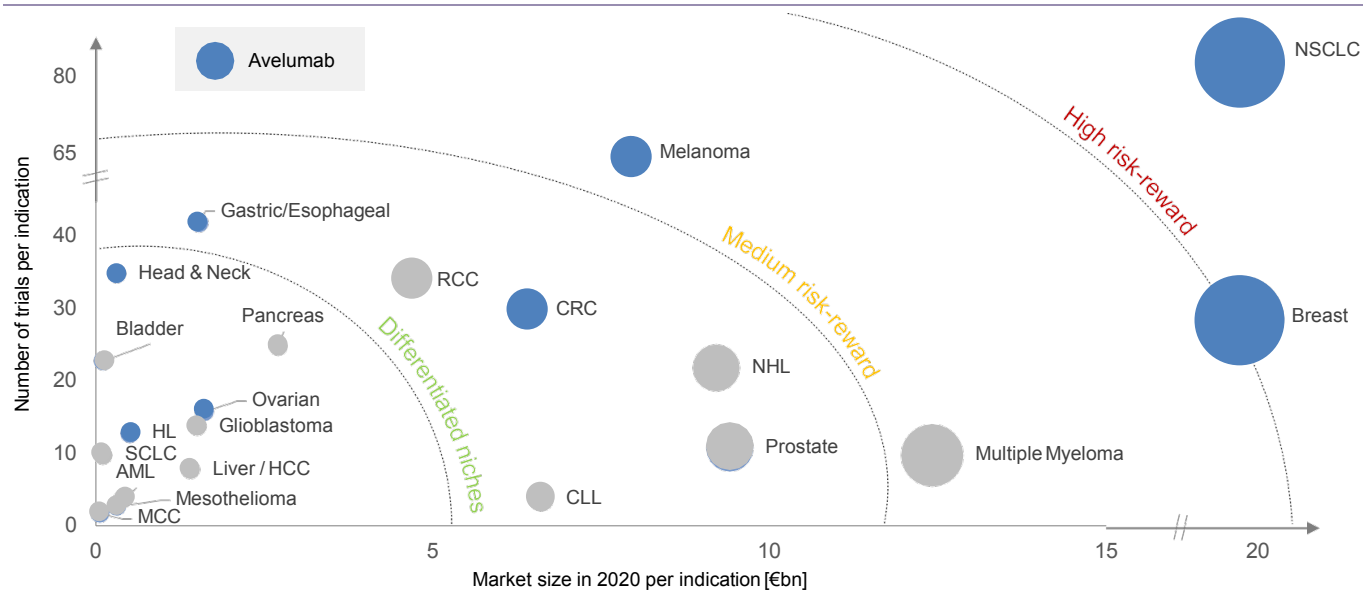
## 4.3. The interest of having Pfizer as a partner

Having major laboratories shouldering R&D and marketing costs for its candidates is clearly a crucial factor for a small biotech company, but it remains to be seen whether they are good partners. What can they provide for Cellectis? And at what point will the platform be strategic for this partner? In order to answer some of these questions, analysing Pfizer's current positioning in the immuno-oncology field and its ambitions is important. In addition, based on management's statements, we understand that the segment has very quickly become a priority segment for the big pharma group.

Avelumab: lower potential relative to other PD-1/PD-L1 inhibitors

Pfizer's main spearhead in the immuno-oncology field is undoubtedly avelumab, and anti-PD-L1 developed in partnership with Merck KGaA and like its competitors, the search for combinations based on this type of therapy is part of the strategic focus. That said, note that avelumab is far less well advanced than its peers (BMS, Merck & Co, Roche and AstraZeneca) in markets as important as lung cancer and melanoma. This is probably why Pfizer and Merck KGaA have opted for a fairly targeted strategy to start with: namely to position themselves in smaller yet probably less competitive and less risky markets (e.g.: soft tissue sarcoma, Merkel cell carcinoma etc.).

**Fig. 22: Avelumab (anti-PD-L1) – Targeted indications**




*Source: Merck KGaA, R&D Update Call (Oct 2015)*

While all these initiatives seem pretty intelligent, we doubt that avelumab's potential can be as significant as that of nivolumab or pembrolizumab given that all these control-point inhibitors do not seem very differentiated, at least in monotherapy. In this case, the big winners are above all likely to be the first entrants and those developing the most optimal combinations. However, in this respect, we do not feel that the big pharma's pipeline differs considerably to that of its most direct rivals (see Fig. 19), while it is still too early to make any statements about their prospective best-in-class status (unless they are the first-in-class).

## Cellectis projects could become critical for Pfizer

We cannot rule out the fact that lines could change as new agreements are signed, or following acquisition moves. However, in the current context, we have the clear conviction that Cellectis' CAR T-cells could rapidly become priority projects within Pfizer's immuno-oncology portfolio given its greater capacity for differentiation.

**Fig. 23: Pfizer's main rivals in 'I-O**

| Program | Competitors | Comments |
|---|---|---|
| IDO1 inhibitor (Prec.) | BMS, Merck, Roche, AZN | IDO is an enzyme that creates a suppressive milieu in tumours by promoting Treg formation and activation (thus allowing tumours to escape immune surveillance)<br>Merck/Incyte's epacadostat with pembrolizumab induced a 53% ORR in R/R patients with advanced solid tumours |
| OX40 agonist (Ph I) | Roche, AZN | OX40 is an activating receptor located on the surface of T cells<br>It is said to 1/ augment the clonal expansion of effector and memory populations, 2/ suppress the differentiation and activity of T-regulatory cells, 3/ regulate cytokine production from T cells, DCs, NK cells, etc. |
| Anti-CD137 (Ph I) | BMS, Novartis | CD137 is found on various immune cells including T cells, NK cells and DCs.<br>Engagement of CD137 by an agonist mAb is said 1/ to enhance T cell proliferation, 2/ to provide protection to CD8+ T cells from activation-induced cell death, and 3/ to activate DCs, NK cells and macrophages.<br>Note that some bispecific antibodies also retained CD137 as a target |
| Anti-CCR2 (Ph I) | Chemocentryx | CCR2-bearing cells, such as Myeloid-Derived Suppressive Cells (MDSCs), are thought to be immunosuppressive<br>It is assumed that inhibiting CCR2, and thus the MDSCs controlled by CCR2, could lead to the liberation of the antitumour response and improve overall survival |

*Source: Company Data; Bryan, Garnier & Co ests.*

# 5. UCART19

## 5.1. The group's most de-risked project

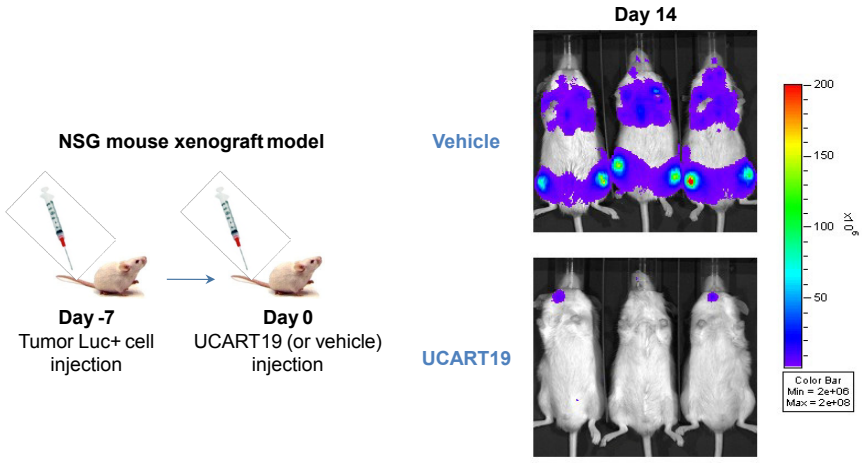
- **ALL: where everything started**

The first UCART19 data indicates similar efficacy to other CAR-Ts and a lack of GVHD

UCART19 is the most advanced allogeneic project in Cellectis' portfolio with a Phase 1 trial currently being initiated under the direction of Pfizer and Servier. It is also the project for which we see the least risk in view of an accumulation of increasingly in-depth data by other CAR-Ts targeting CD19. Efficacy and toxicity data that we have so far above all concern preclinical models, although they at least had the merit of showing that suppression of TCR effectively resulted in a lack of GVHD and that UCART19 could be just as efficient as its autologous peers over a fairly short period.

In addition, a young girl of 11 months, suffering from the disease was recently successfully treated with UCART19 in the context of a compassionate treatment. Refractory to all current treatments available for acute lymphoblastic leukaemia, we understand that her immune system was far too weakened for an autologous approach to be applied (and for this reason doctors at the Great Ormand Street Hospital in London turned to Cellectis in order to have rapid and urgent access to its technology. All of this needs to be confirmed under the framework of a wider-scale clinical study, but we believe that these various factors have been significant in the development's de-risking.

**Fig. 24: UCART19 preclinical results in ALL**




*Source: Cellectis*

DSMB analysis should provide qualitative factors that would reassure on the safety profile

The question remains as to when we might have a clearer idea of the candidate's safety profile. Clearly results from Phase 1 in 2017e will be the real decider, but we also believe that future feedback from the DSMB should also provide qualitative factors that should reassure on the project's safety profile, and consequently lead to stockmarket jumps.

- **However, the real potential lies in CLL and NHL**

Heading for a V4 integrating a PD-1 K-O in order to better address CLL and NHL?

Given that the number of patients suffering each year is far greater for CLL cases (chronic lymphoid leukaemia) and NHL (non-Hodgkin's lymphomas), it is hardly surprising that market potential is higher too, especially since CAR-T CD19s have also proven their efficacy in these areas.

The company has not yet communicated on an eventual development of UCART19 in non-Hodgkin's lymphomas, although a number of rivals (especially Novartis and Juno Therapeutics have collected fairly promising data in various sub-types of blood cancer and are also considering combinations with PD-1/PD-L1 inhibitors in order to approach the 90%-mark in terms of complete response. Knowing this, we ask ourselves whether Pfizer and Servier will not rapidly be asking for a new version including a PD-1 gene knock-out in order to strengthen the competitiveness of UCART19 relative to current and future rival developments. In any case, we are highly convinced that Cellectis' partners should not neglect a significant market, for which we already have clinical data validating the potential of CAR-T CD19.

## 5.2. Potential sales of almost EUR1.2bn

We are starting out today with the principle that UCART19 and all the other projects developed by Cellectis will above all be last-line alternatives given their toxicity potential (CRS, neurotoxicity etc.). We have then assumed 1) pricing of USD150,000 per patient for the US and EUR90,000 for the rest of the world and 2) market share gains of 40% in ALL, based on the principle that the efficacy and safety profiles are fairly similar to those of other CAR-T anti-CD19s.

Another important point: we have chosen to integrate growth prospects related to the development in NHL, albeit with slightly less aggressive sales penetration assumptions than in ALL and CLL (although we could review this if a V4 were actually to be developed).

**Fig. 25: UCART19 sales forecasts in ALL treatment**

| | 2021e | 2022e | 2023e | 2024e | 2025e | 2026e |
|---|---|---|---|---|---|---|
| CD19+ patients | 95% | | | | | |
| % 3rd and 4th lines | 20% | | | | | |
| UCART19 - Cost per patient in the US (USD) | 150,000 | | | | | |
| UCART19 - Cost per patient in Europe (EUR) | 90,000 | | | | | |
| | | | | | | |
| Market penetration in the US (%) | 5% | 10% | 20% | 30% | 40% | 40% |
| Market penetration in Europe (%) | 5% | 10% | 20% | 30% | 40% | 40% |
| Market penetration in the ROW (%) | 5% | 10% | 20% | 30% | 40% | 40% |
| | | | | | | |
| **UCART19 - ALL - Revenues (EURm)** | **22** | **45** | **91** | **138** | **186** | **188** |

*Source: Bryan, Garnier & Co ests.*

### Fig. 26: UCART19 sales forecasts in CLL treatment

| | 2022e | 2023e | 2024e | 2025e | 2026e | 2027e |
|---|---|---|---|---|---|---|
| US incidence of CLL | 16,618 | 16,784 | 16,952 | 17,122 | 17,293 | 17,466 |
| Europe incidence of CLL | 23,641 | 23,877 | 24,116 | 24,357 | 24,600 | 24,846 |
| ROW incidence of CLL | 21,443 | 21,657 | 21,874 | 22,092 | 22,313 | 22,537 |
| | | | | | | |
| CD19+ | 95% | | | | | |
| % 3rd and 4th lines | 20% | | | | | |
| UCART19 - Cost per patient in the US (USD) | 150,000 | | | | | |
| UCART19 - Cost per patient in Europe (EUR) | 90,000 | | | | | |
| | | | | | | |
| Market penetration in the US (%) | 5% | 10% | 20% | 30% | 35% | 35% |
| Market penetration in Europe (%) | 5% | 10% | 20% | 30% | 35% | 35% |
| Market penetration in the ROW (%) | 5% | 10% | 20% | 30% | 35% | 35% |
| | | | | | | |
| **UCART19 - CLL - Revenues (EURm)** | **64** | **130** | **263** | **398** | **469** | **473** |

*Source: Bryan, Garnier & Co ests.*

### Fig. 27: UCART19 sales forecasts in NHL

| | 2022e | 2023e | 2024e | 2025e | 2026e | 2027e |
|---|---|---|---|---|---|---|
| US incidence of NHL (DLBCL, FL) | 46,220 | 46,682 | 47,149 | 47,620 | 48,096 | 48,577 |
| Europe incidence of NHL (DLBCL, FL) | 33,734 | 34,071 | 34,412 | 34,756 | 35,103 | 35,454 |
| ROW incidence of NHL (DLBCL, FL) | 32,164 | 32,486 | 32,811 | 33,139 | 33,470 | 33,805 |
| | | | | | | |
| CD19+ | 95% | | | | | |
| % 3rd and 4th lines | 20% | | | | | |
| UCART19 - Cost per patient in the US (USD) | 150,000 | | | | | |
| UCART19 - Cost per patient in Europe (EUR) | 90,000 | | | | | |
| | | | | | | |
| Diffuse large B cell lymphomas | | | | | | |
| Market penetration in the US (%) | 5% | 10% | 20% | 25% | 30% | 30% |
| Market penetration in Europe (%) | 5% | 10% | 20% | 25% | 30% | 30% |
| Market penetration in the ROW (%) | 5% | 10% | 20% | 25% | 30% | 30% |
| Folicular lymphomas | | | | | | |
| Market penetration in the US (%) | 5% | 10% | 15% | 20% | 25% | 25% |
| Market penetration in Europe (%) | 5% | 10% | 15% | 20% | 25% | 25% |
| Market penetration in the ROW (%) | 5% | 10% | 15% | 20% | 25% | 25% |
| | | | | | | |
| **UCART19 - NHL - Revenues (EURm)** | **103** | **208** | **386** | **496** | **608** | **614** |

*Source: Bryan, Garnier & Co ests.*

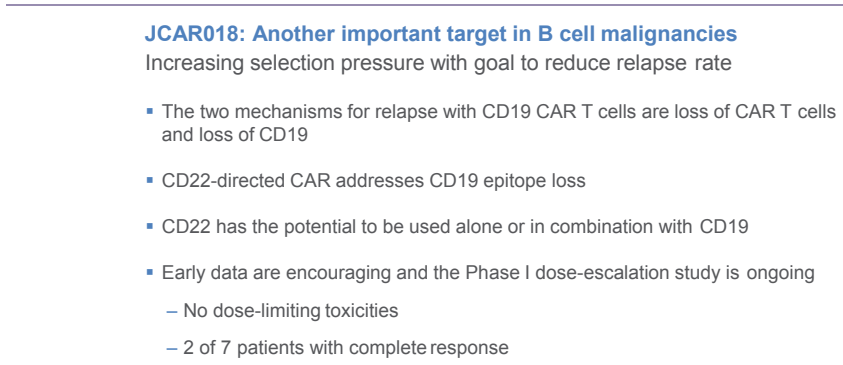
## 5.3. UCART22 or how to complement UCART19

CD22: a way of getting round the loss of expression of CD19

Admittedly, the various CAR-T CD19s have generated impressive complete response rates in ALL. However, this does not prevent certain patients from going into relapse, especially following loss of CD19 expression. With this in mind, Cellectis decided to develop a CAR-T targeting CD22 (for which the expression pattern is fairly similar to CD19) and which could be used as an alternative in relapse patients.

The strategy looks fairly smart and the fact that Juno Therapeutics has also chosen this target with JCAR018, merely validates our positive impression. The first clinical data for JCAR018 is encouraging (two complete responses out of seven patients enrolled in a Phase I with an escalating dose). However, as with all the other approaches, a bit more time and perspective is needed before we can have a genuine idea of this product's potential (is the antigen more volatile? or in other words, is the risk of premature relapse not higher?).

**Fig. 28: Development rationale for a CAR-T CD22**




*Source: Juno Therapeutics*

Note that CD22 is also a target retained by Pfizer for the construction of inotuzumab ozogamicin, a drug conjugated antibody. Given that the approach includes a cytotoxic factor in order to make the anti-tumour action of mAbs potentially possible, eventual cross-readings are fairly limited in our view. However, note that this compound nevertheless generated fairly deep tumour responses in monotherapy in patients in last-line treatment and suffering from ALL (CR: 80% vs 33% for the group receiving chemotherapy).

# 6. UCART38: an attractive card to play in myeloma

**UCART38 targets CD38 and integrates a PD-1 gene knock-out.** The fact that the group has chosen this antigen has three major implications in our view: 1) it should enable Cellectis to position itself in an indication that is still not properly addressed by other CARs, but which is nevertheless potentially very lucrative, 2) some of the development is de-risked by the data generated by daratumumab (an mAbs anti-CD38), as well as the recent FDA approval, 3) while this remains very theoretical, UCART38 could potentially become a best-in-class for last line treatments.

## 6.1. Targeting a market still little addressed by other CAR-Ts

**Multiple myeloma is not really addressed by the CAR-Ts currently in development** given the low expression of CD19 and CD22 proteins in this indication. Novartis' management nevertheless confirmed that blood cancer was among the interesting indications for its platform, but that this would probably involve the selection of an entirely different protein for the construction of a new synthetic receptor. Although the eventual targets were not unveiled, the fact that antibodies targeting CD38 and CS1 have generated good tumour responses suggest that they are clearly part of the Swiss laboratory's scope of consideration.

First implication: extending the addressable market for CAR-Ts to myeloma

Whatever the case, implications in terms of addressable market are significant, with the incidence of myeloma being far more important for ALL or even CLL (25,000 new cases just for the US vs. 7,000 and 15,000 respectively). We would not be surprised either if this blood cancer gradually became a priority target market for the various laboratories developing CAR-Ts.

**Fig. 29: Expression of CD38 depending on cancer type**

| Indication | CD38 expression | Top 7 countries |
|---|---|---|
| Chronic Myeloid Leukaemia (CML) | 60% | 11,000 |
| Acute Lymphoblastic Leukaemia (ALL) | 75% | 12,000 |
| Chronic Lymphocytic Leukaemia (CLL) | 20-45% | 33,000 |
| Multiple Myeloma (MM) | 98% | 48,000 |
| Non-Hodgkin Lymphomas (NHL) | 50% | 100,000 |

*Source: Genmab; Morphosys;; Bryan, Garnier & Co ests.*

## 6.2. "Harder, better, faster, stronger"

- **A clear interest for CD38**

Clinical data for daratumumab validate the interest of CD38 as a therapeutic target

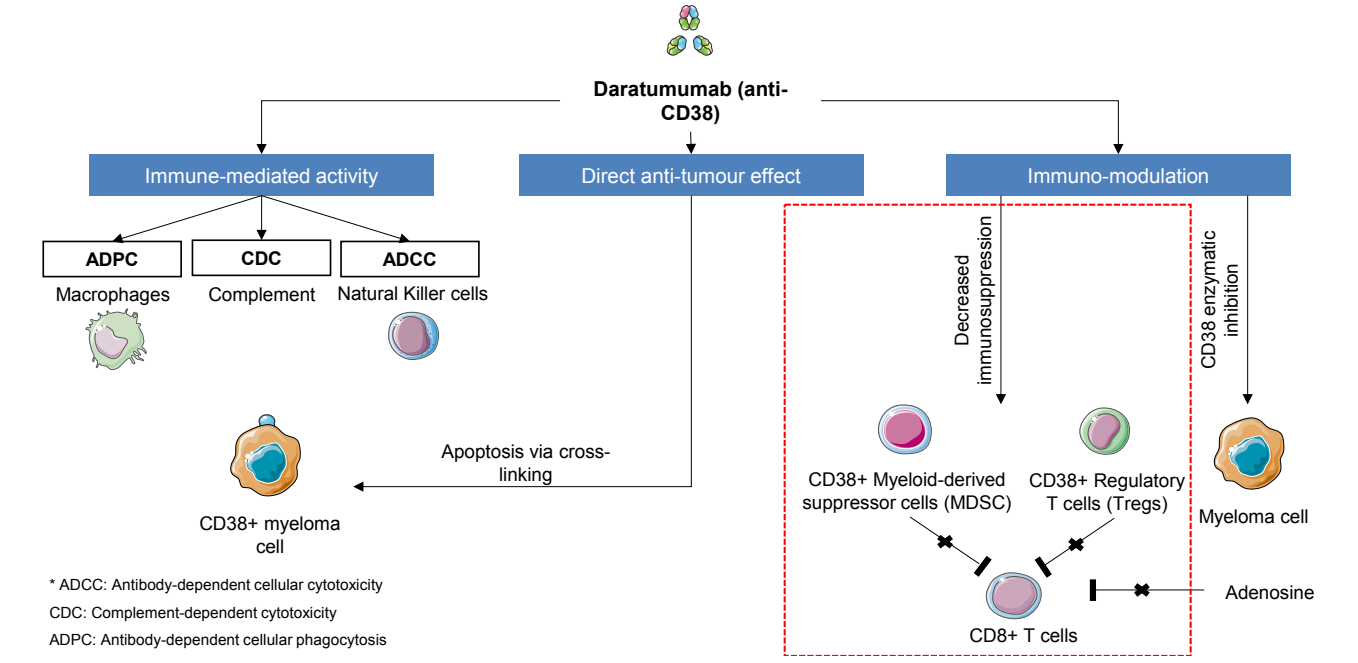
As already discussed in our Genmab initiation report (The Force Awakens!), the following are reminders of the interest of targeting the CD38 protein in this indication:

- CD38 is generally overexpressed by virtually all myeloma cells and by a fairly limited number of healthy cells. In addition, its expression is thought to be fairly stable despite repeated treatments (responding patients remain so on an extremely sustainable basis) and is also

thought to concern immunosuppressive cells such as Tregs and MDSC (which is what would explain the positive effect that daratumumab has on pre-existing immune responses.

- The clinical efficacy data obtained is among the best ever seen for myeloma.
  At the last ASH congress, Genmab notably presented a combined analysis of two studies (SIRIUS and GEN501) having enrolled highly pre-treated patients (average of five previous therapies) and where dara had been administered in monotherapy. If we only retained one figure it would be average survival: 19.9 months after an average follow-up of 14.8 months, which is considerably higher than all historical controls seen so far (7-8 months with treatments such as steroids/cyclophosphamide and 10 months for Amgen's Kyprolis).

**Fig. 30: Daratumumab – action mechanism**




*Source: Adapted from Genmab R&D day (Dec 2015); Bryan, Garnier & Co ests.*

### Going further than therapeutic antibodies in tumour responses

CAR-T CD38s could potentially induce deeper responses than with anti-CD38 antibodies

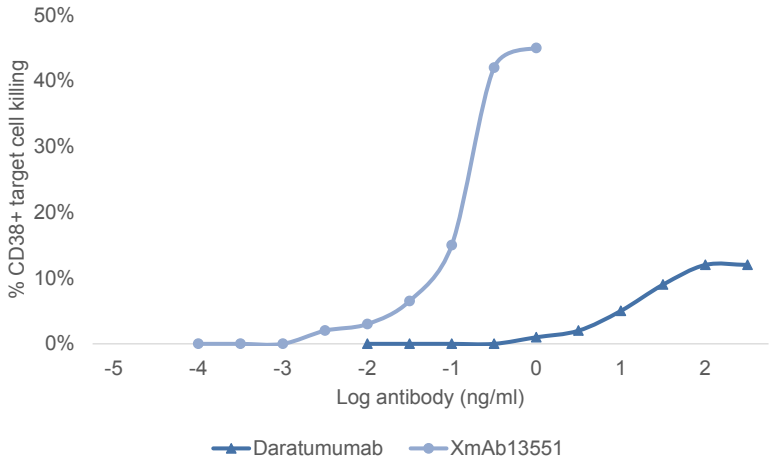
We believe that UCART38 could induce better responses than traditional mAbs. Clinical data will obviously be the real decider, but we would note that 1) T CD8+ cells are by definition the players in our immune system with the greatest anti-tumour powers, 2) use of CAR-Ts could help get round numerous inherent immune checkpoints and eventual issues that could be encountered upstream of the immune response (alteration of MHC molecule expression etc.).

Proof is that 1) CAR-Ts directed against CD19s have generated a larger number of complete responses than mAbs such as MOR208 (which only generated an ORR of 38% in R/R patients suffering from CLL), 2) a CD3xCD38 such as XmAb13551 seems more efficient than daratumumab *in vitro* (we would also note that Amgen has signed an agreement with Xencor in order to get its hands on this bispecific and other projects (upfront: USD45m, potential payments of USD1.7bn).

The icing on the cake is that the PD-1 gene knock-out should only strengthen the efficacy of this approach given the significance of expression of the PD-L1 ligand in this indication (> 90%).

However, the tumour micro-environment is very complex and we believe that chances of success could be maximised thanks to the administration of chemotherapies such as fludarabine/doxorubicin (bearing in mind that the dCK knock-out should increase UCART38's resistance to these lymphodepleting therapies).

**Fig. 31: *in vitro* results of XmAb13551 vs daratumumab (myeloma)**




*Source: Adapted from SY Chu et al, ASH 2014*

## 6.1. Upside to be confirmed in NHL

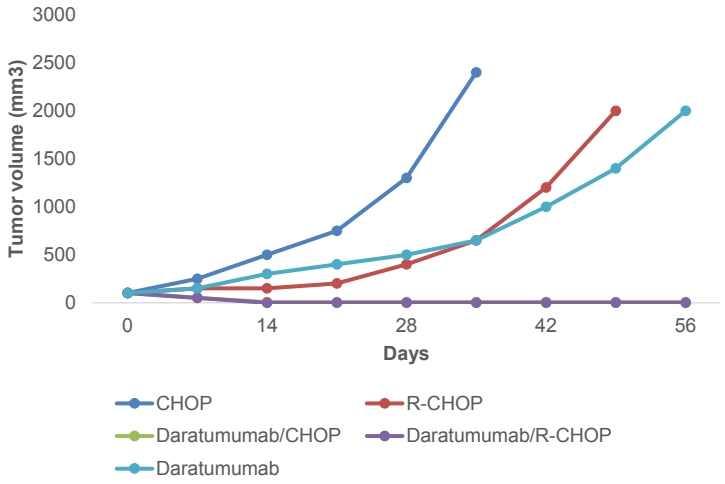
CD38 could also be extremely interesting in NHL

Several scientific research articles have presented CD38 as an interesting protein in the treatment of B non-Hodgkin's lymphomas given the extent of its expression and its low variability, which are why parallels are often made with CD19.

We will see whether new data can validate this thesis, but various *in vivo* and *in vitro* experiments have shown that 1) CAR-T anti-CD38s are capable of destroying cells resistant to -T anti-CD19, and that 2) the combination of the two options is far more efficient than each one taken separately (Mihara et al, 2009 & 2010). The fact that UCART38 also neutralises formation of the PD-1 protein is also interesting. Checkpoint blockers such as nivolumab (anti-PD-1) have indeed generated attractive data in monotherapy and in refractory or relapse patients with various sub-types of NHL (Fig. 33).

However, caution is the mother of safety and until we have more data from Genmab/JNJ or Sanofi, we believe that there is no reason (yet) to be overly optimistic on these developments.

**Fig. 32: Daratumumab – preclinical results in DLBCL**




*Source: Bryan, Garnier & Co. ests. Adpated from Genmab R&D day (Dec 2014)*

**Fig. 33: Efficacy of nivolumab (anti-PD-1) in various types of lymphomas**

| Tumour | n | CR (%) | PR (%) | SD (%) | PFS 24-weeks |
|---|---|---|---|---|---|
| Diffuse Large B Cell Lymphoma (DLBCL) | 11 | 9% | 27% | 27% | 24% |
| Follicular Lymphoma (FL) | 10 | 10% | 30% | 60% | 68% |
| Other B cell Lymphoma | 8 | 0% | 0% | 63% | 38% |
| Primary Mediastinal B Cell Lymphoma | 2 | 0% | 0% | 100% | 0% |
| Mycosis Fungoides (MF) | 13 | 0% | 15% | 69% | 39% |
| Peripheral T Cell Lymphoma (PTCL) | 5 | 0% | 40% | 0% | 30% |
| Multiple Myeloma (MM) | 27 | 0% | 0% | 67% | 15% |
| Chronic Myelogenous Leukaemia | 1 | 0% | 0% | 100% | 100% |

*Source: Lesokhin et al, ASH 2014*

## 6.2. The group's potential blockbuster

**We expect a level of revenues close to EUR1.3bn,** bearing in mind that the majority of the value lies in multiple myeloma (EUR1.0bn precisely) in view of various proof of concepts that have been accumulated with daratumumab and PD-1/PD-L1 inhibitors. Clearly, this does not mean that the UCART38 clinical trials will necessarily result in huge successes since numerous questions remain unanswered today (what toxicity profile? what efficacy for a CAR-T with so many knock-out genes?).

In addition, we believe that the addressable market should notably include refractory patients or those in relapse following first-line treatments including proteasome inhibitors. There are two reasons for this, namely that patients treated with anti-CD38 antibodies theoretically present a higher risk of losing expression of the antigen, and in the majority of cases, these same patients have also received immunomodulators (lenalidomide, pomalidomide) and these tend to upregulate expression of CD38 (Boxhammer et al, 2015)…

In addition to this, we are fairly cautious in our forecasts implying non-Hodgkin's lymphomas, at least pending clinical data concerning daratumumab in this indication. On the other hand, we have voluntarily included DLBCLs whereas the Phase I study only limits itself to MCLs given that the

rationale behind an extension such as this seems fairly solid for all the reasons already mentioned and that management does not seem to be closed to this eventuality.

**Fig. 34: UCART38 - sales forecasts in MM**

| | 2022e | 2023e | 2024e | 2025e | 2026e | 2023e | 2022e | 2027e |
|---|---|---|---|---|---|---|---|---|
| US incidence of MM | 29,377 | 29,670 | 29,967 | 30,267 | 30,569 | 30,875 | 31,184 | 31,496 |
| Europe incidence of MM | 38,276 | 38,659 | 39,046 | 39,436 | 39,830 | 40,229 | 40,631 | 41,037 |
| ROW incidence of MM | 44,554 | 44,999 | 45,449 | 45,904 | 46,363 | 46,826 | 47,295 | 47,768 |
| | | | | | | | | |
| CD38+ patients | 90% | | | | | | | |
| % 3rd and 4th lines | 25% | | | | | | | |
| UCART38 - Cost per patient in the US (USD) | 150,000 | | | | | | | |
| UCART38 - Cost per patient in Europe (EUR) | 100,000 | | | | | | | |
| | | | | | | | | |
| Market penetration in the US (%) | 1% | 10% | 20% | 30% | 35% | 35% | 35% | 35% |
| Market penetration in Europe (%) | 1% | 10% | 20% | 30% | 35% | 35% | 35% | 35% |
| Market penetration in the ROW (%) | 0% | 1% | 10% | 20% | 30% | 35% | 35% | 35% |
| | | | | | | | | |
| **UCART38 - MM - Revenues (EURm)** | **18** | **188** | **462** | **751** | **955** | **1,017** | **1,027** | **1,038** |

*Source: Bryan, Garnier & Co ests.*

**Fig. 35: UCART38 – sales forecasts in NHL**

| | 2022e | 2023e | 2024e | 2025e | 2026e | 2023e | 2022e | 2027e |
|---|---|---|---|---|---|---|---|---|
| US incidence of DLBCL, FL | 34,665 | 35,012 | 35,362 | 35,716 | 36,073 | 36,434 | 36,798 | 37,166 |
| Europe incidence of DLBCL, FL | 25,300 | 25,553 | 25,809 | 26,067 | 26,328 | 26,591 | 26,857 | 27,125 |
| ROW incidence of DLBCL, FL | 24,123 | 24,364 | 24,608 | 24,854 | 25,103 | 25,354 | 25,607 | 25,863 |
| | | | | | | | | |
| CD38+ patients | 50% | | | | | | | |
| % 3rd and 4th lines | 25% | | | | | | | |
| UCART38 - Cost per patient in the US (USD) | 150,000 | | | | | | | |
| UCART38 - Cost per patient in Europe (EUR) | 100,000 | | | | | | | |
| | | | | | | | | |
| Market penetration in the US (%) | 1% | 5% | 10% | 15% | 20% | 25% | 25% | 25% |
| Market penetration in Europe (%) | 1% | 5% | 10% | 15% | 20% | 25% | 25% | 25% |
| Market penetration in the ROW (%) | 0% | 1% | 5% | 10% | 15% | 20% | 25% | 25% |
| | | | | | | | | |
| **UCART38 - NHL - Revenues (EURm)** | **9** | **49** | **108** | **171** | **236** | **302** | **321** | **324** |

*Source: Company Data; Bryan, Garnier & Co ests.*

# 7. UCARTCS1

**UCARTCS1 is a CAR-T anti-CS1 presenting a PD-1 and CS1 knock-out** that Cellectis is likely to develop in multiple myeloma in particular. The strategic rationale behind this project is the same as with CD38: developing a candidate capable of addressing a market that is ultimately virtually inaccessible to CAR-T CD19s. That said, the protein targeted is very different and we will see that the implications are strong for the efficacy and toxicity profile.

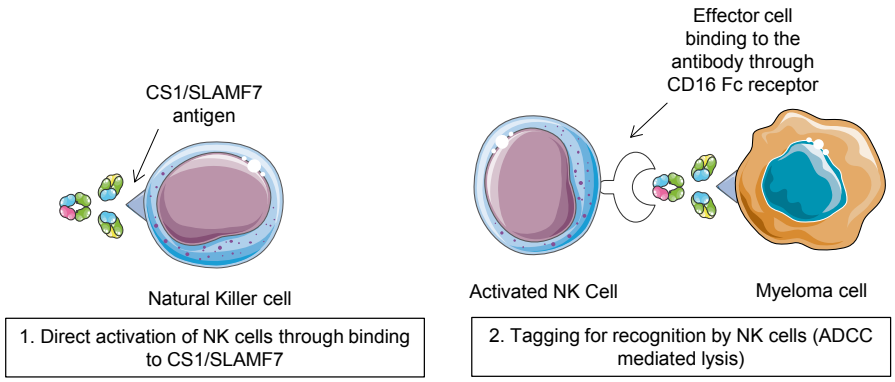
## 7.1. CS1: a less attractive target than CD38?

CS1: a target validated by approval of elotuzumab in myeloma

CS1/SLAMF7 is another protein highly expressed on the surface of myeloma cells (in more than 95% of cases) and to a lesser extent on natural killer cells and certain lymphocytes.

**To our eyes, this target has been validated by the recent approval of BMS/AbbVie's Empliciti (elotuzumab).** The precious sesame was notably obtained thanks to a multi-centric, randomised and open-label Phase III trial. In particular this showed that the addition of elotuzumab to lenalidomide/dexamethasone helped reduce the risk of progression or death by 30% over a two-year period (HR: 0.70, p=0.0004). Response rates were far more significant in the active group (79% vs. 66%) and especially in terms of partial responses and very good partial responses. Contrary to what we might think, the number of side effects was fairly similar between the two branches of the study.

**Fig. 36: Elotuzumab (anti-CS1 antibody) – action mechanism**




*Source: Bryan, Garnier & Co, ests.*

However, CD38 seems to be a target with a wider spectrum of implications

However, the reality is probably slightly less idyllic than it looks. Indeed, "elo" generated no response in monotherapy in highly pre-treated patients, contrary to a lot of other candidate drugs (see Fig. 36). Responses were generally improved under the framework of combinations with therapies such as lenalidomide, but overall they remain far below those of daratumumab (which could be explained by the immuno-modulation it induces and the greater number of anti-tumour pathways taken).

Note nevertheless that **BMS initiated a Phase I trial assessing elotuzumab in combination with lirilumab (an anti-KIR developed by Innate Pharma) or urelumab (an anti-CD137)**, and theoretically, data from this study could be published as of the end of this year. The aim is clearly to go further in tumour regression, although we also believe that the need to stand out from the crowd is even greater in a backdrop where combinations above all concern Revlimid (lenalidomide)… In this context, we would not be surprised either if Merck & Co announced the initiation of a new trial

implying pembrolizumab (anti-PD-1) and its anti-GITR in myeloma and other haematological tumours.

**Fig. 37: Myeloma - results of various agents in monotherapy**

| Drugs | Study | Settings | Responses |
|---|---|---|---|
| Carfilzomib | PX-171-003-A1 | R/R patients (median of 5 prior lines of therapy) | ORR: 23.7%, CR: 0.4%, VGPR: 5.0%, PR: 18.3% |
| Carfilzomib | FOCUS | R/R patients (median of 5 prior lines of therapy) | ORR: 19.1% |
| Daratumumab | SIRIUS (16 mg/kg) | Double refractory (median of 5 prior lines of therapy) | ORR: 29.2%, CR: 3%, VGPR: 9%, PR: 17% |
| Daratumumab | GEN501 Part 2 (16 mg/kg) | R/R patients (median of 4 prior lines of therapy) | ORR: 35%, CR: 10%, VGPR: 5%, PR: 20% |
| SAR650984 | NCT01084252(≥ 10 mg/kg) | R/R patients (median of 5 prior lines of therapy) | ORR: 33%, CR: 11%, PR: 22% |
| Pomalidomide | NCT00833833 | R/R patients (median of 5 prior lines of therapy) | ORR: 18%, CR: 2%, PR: 16% |
| Elotuzumab | NCT00425347 | R/R patients (median of 5 prior lines of therapy) | ORR: 0%, SD: 26.5% |

*Source: Companies data*

**Fig. 38: Myeloma - efficacy results of various combinations with lenalidomide/dexamethasone**

| Drugs | Study | N | Settings | Responses |
|---|---|---|---|---|
| Daratumumab | GEN503 Part 1 | 16 (16 mg/kg | R/R patients with 1-4 prior lines (median: 2) | ORR: 100% (CR: 31%, VGPR: 46%, PR: 23%) |
| Daratumumab | GEN503 Part 2 | 32 (16 mg/kg) | R/R patients with 1-4 prior lines (median: 2) | ORR: 87% (CR: 7%, VGPR: 43%, PR: 37%) |
| Elotuzumab | Study 1703 | 36 (10 mg/kg) | R/R patients with 1-3 prior lines (median: 2) | ORR: 92% (CR: 14%, VGPR: 47%, PR: 31%) |
| Elotuzumab | ELOQUENT-2 | 646 (10 mg/kg) | R/R patients with 1-3 prior lines (median: 2) | ORR: 79% (CR: 4%, VGPR: 28%, PR: 46%) |
| Carfilzomib | ASPIRE | 396 | R/R patients with 1-3 prior lines (median: 2) | ORR: 87.4% (CR: 31.8%, VGPR or PR: 70.4%) |

*Source: Companies data*

## 7.2. Potential sales of EUR550m

We have assumed that UCARTCS1 is a slightly less lucrative project than UCART38 given that expression of the target antigen is ultimately fairly low outside multiple myeloma (in other words, the addressable market base is smaller) and the efficacy and toxicity profile that we see is unlikely to be as impressive as for UCART38. In this context, we have assumed market share gains of 20% (vs. 35% for UCART38) in third and fourth line treatments.

**Fig. 39: UCARTCS1 - sales forecasts in myeloma**

| | 2022e | 2023e | 2024e | 2025e | 2026e | 2027e |
|---|---|---|---|---|---|---|
| US incidence of MM | 29,377 | 29,670 | 29,967 | 30,267 | 30,569 | 30,875 |
| Europe incidence of MM | 38,276 | 38,659 | 39,046 | 39,436 | 39,830 | 40,229 |
| ROW incidence of MM | 44,554 | 44,999 | 45,449 | 45,904 | 46,363 | 46,826 |
| | | | | | | |
| CS1+ patients | 95% | | | | | |
| % 3rd and 4th lines | 25% | | | | | |
| UCARTCS1 - Cost per patient in the US (USD) | 150,000 | | | | | |
| UCARTCS1 - Cost per patient in Europe (EUR) | 100,000 | | | | | |
| | | | | | | |
| Market penetration in the US (%) | 1% | 5% | 10% | 15% | 20% | 20% |
| Market penetration in Europe (%) | 1% | 5% | 10% | 15% | 20% | 20% |
| Market penetration in the ROW (%) | 0% | 5% | 10% | 15% | 20% | 20% |

| | | | | | | |
|---|---|---|---|---|---|---|
| **UCARTCS1 - MM - Revenues (EURm)** | **19** | **147** | **298** | **451** | **607** | **613** |

*Source: Bryan, Garnier & Co ests.*

# 8. UCART123

**UCART123 notably targets CD123, a protein that is apparently highly expressed by AML cells** (acute myeloid leukaemia). Here again, Cellectic still has all rights to development and marketing of the product. So far we have no clinical data that would help fully assess the drug's potential, but one thing is sure: given the competitive backdrop in which it is present, upside potential could be far greater than in ALL.

## 8.1. A foot in AML

- **A still largely unmet medical need**

A less competitive backdrop that ALL, CLL and NHL

The competitive backdrop has changed massively for haematological tumours such as CLL and NHL. However, this is clearly not yet the case for AML, with regimes based on cytarabine and anthracyline remaining the standard at present (although they were approved during the 1970s). While these are fairly efficient, we would nevertheless point out that the side effects they produce are at the root of a high level of mortality (20-50%), and mean that a large share of patients cannot take the drug. On the other hand, the disease's heterogeneous nature combined with the fact that patients are often very old, were probably significant obstacles for eventual new therapies.

This therapeutic gap could be partly filled by 1) small molecules such as venetoclax, which recently received breakthrough therapy status (ORR in combo with hypomethylating agents: 70-75% in first-line patients not eligible for standard chemotherapy), or even 2) tyrosine kinase inhibitors such as sorafenib for FLT3+ patients (ORR in combination with 5-azacitidine: 46% in pre-treated patients). However, it is difficult to say whether these potential new therapies would be a genuine panacea…

- **Why target CD123?**

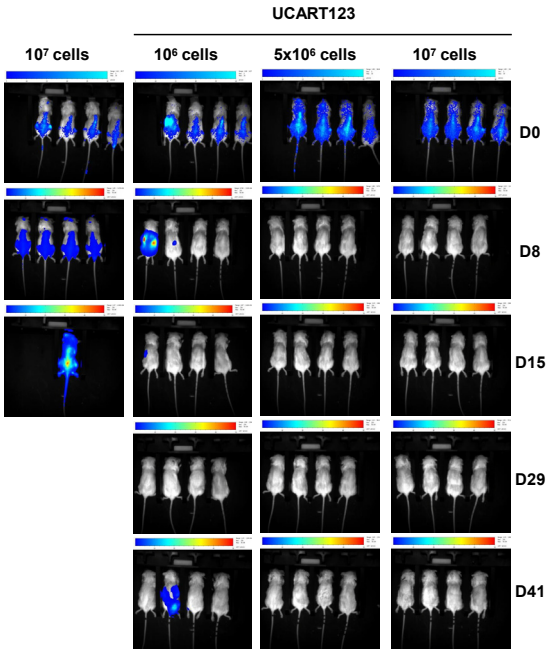
CD123: a target partly validated by other therapeutic approaches

**CD123 is one of the rare proteins overexpressed by AML cells (> 90% of cases)**, and it is very probably for this reason that several cytotoxic antibodies, bispecifics or ADCs in development target it (although data in humans is still lacking). Preclinical results obtained with UCART123 nevertheless bode well from an efficacy standpoint with all animals used having enjoyed complete responses that are seemingly fairly stable. It remains to be seen if the expression (albeit weak) of the protein by various stem cells could hamper things to come (what impact on myelopoiesis, or inversely could greater expression at this level be necessary to eradicate the disease's start point?).

However, beyond the factors inherent in this project, note importantly that CD123 is not the only antigen of interest for this indication. For example, CD33 seems to be making a return despite the failure of gemtuzumab ozogamicin (an ADC anti-CD33) and its withdrawal from the market in 2010. In addition to being highly expressed on the surface of cancer cells, it would appear that its expression persists even in R/R patients after treatment such as gemtuzumab (thereby suggesting that the loss of this antigen is not a factor that can commonly explain a patient's relapse).

Whatever the case, we believe that the addition of a switch-off mechanism should not be a luxury in order to limit an excess of toxicity.

**Fig. 40: UCART123 preclinical results in AML**




*Source: Cellectis*

## 8.2. Heading for peak sales of EUR500m

The project looks fairly attractive on paper, given the target retained for the synthetic receptor as well as the therapeutic landscape which looks far less competitive than for other blood cancers. However, we should not forget that 1) we still do not have proof of concept (whether in terms of CAR-Ts or other approaches) that would affirm that CD123 is indeed an optimal target for AML treatment, and 2) the first data obtained belongs above all to the pre-clinical field. With this in mind, we have decided to retain an assumption for market share gains of 35% for all regions considered despite low competitive intensity, but a lower probability of success than for other projects.

**Fig. 41: UCART123 sales forecasts in AML**

| | 2022e | 2023e | 2024e | 2025e | 2026e | 2027e |
|---|---|---|---|---|---|---|
| US incidence of AML | 16,082 | 16,243 | 16,405 | 16,569 | 16,735 | 16,902 |
| Europe incidence of AML | 20,220 | 20,423 | 20,627 | 20,833 | 21,042 | 21,252 |
| ROW incidence of AML | 16,082 | 16,243 | 16,405 | 16,569 | 16,735 | 16,902 |
| | | | | | | |
| CD123+ patients | 95% | | | | | |
| % 3rd and 4th lines | 25% | | | | | |
| UCART123 - Cost per patient in the US (USD) | 150,000 | | | | | |
| UCART123 - Cost per patient in Europe (EUR) | 90,000 | | | | | |
| | | | | | | |
| Market penetration in the US (%) | 1% | 5% | 10% | 20% | 30% | 35% |
| Market penetration in Europe (%) | 1% | 5% | 10% | 20% | 30% | 35% |
| Market penetration in the ROW (%) | 0% | 5% | 10% | 20% | 30% | 35% |
| | | | | | | |
| **UCART123 - AML - Revenues (EURm)** | **10** | **70** | **141** | **285** | **432** | **509** |

*Source: Bryan, Garnier & Co ests.*

# 9. Heading for new partnerships?

The fact that Cellectis can develop its own projects while relying on Pfizer's data base is a unique situation that the French company could leverage extensively. UCART38 is nevertheless a specific case, since Pfizer has a pre-emptive right to this asset (although this does not mean that interest could be lower from other pharma groups). Companies that are not yet developing CAR-Ts are rare and quite surprisingly, two leaders in the immuno-oncology sector are among these, namely Roche and Bristol-Myers Squibb. And then there is the question of Sanofi…

If a new agreement should be signed, the financial terms are likely to be far more lucrative than the latest deal with Pfizer

In all cases, **we believe that the financial terms of an eventual agreement with one of these big pharma groups should be better than the deal with Pfizer and Servier,** given that: 1) the current proprietary projects benefit from qualities that have not been seen at any other biotech company (allogenicity, PD-1 KO, etc.) 2) the development plan is partly de-risked (i.e. once clinical data is published), 3) the deal tying Celgene and Juno probably had an inflationary effect.

**Fig. 42: Financial terms of recent deals implying CAR-T / TCR**

| Company | Partner | Financial terms |
|---|---|---|
| Celgene | Juno Therapeutics | Upfront: USD150m, equity investment: c.USD850m, milestones payments: nd |
| GlaxoSmithKline | Adaptimmune | Upfront: none, milestones payments: USD230m per project |
| Amgen | Kite Pharma | Upfront: USD60m, milestones payments: USD525m |
| JNJ | Transposagen | Upfront: USD292m, milestones payments: USD292m per project |

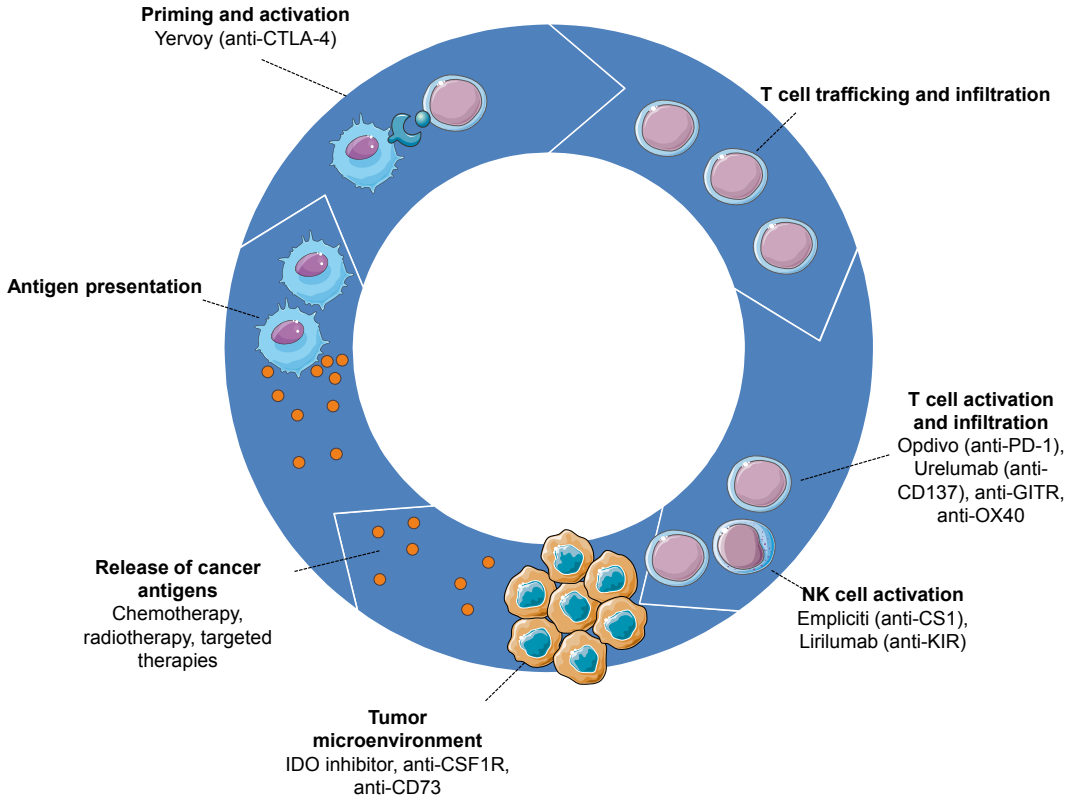
*Source: Company Data; Bryan, Garnier & Co ests.*

- **Bristol-Myers Squibb and Roche: fast leaders with no CAR-T**

Fairly strangely, the three current leaders in the anti-cancer immunotherapy segment have yet to start developing CAR-T. But does this mean that these three major names will continue to neglect such highly promising approaches?

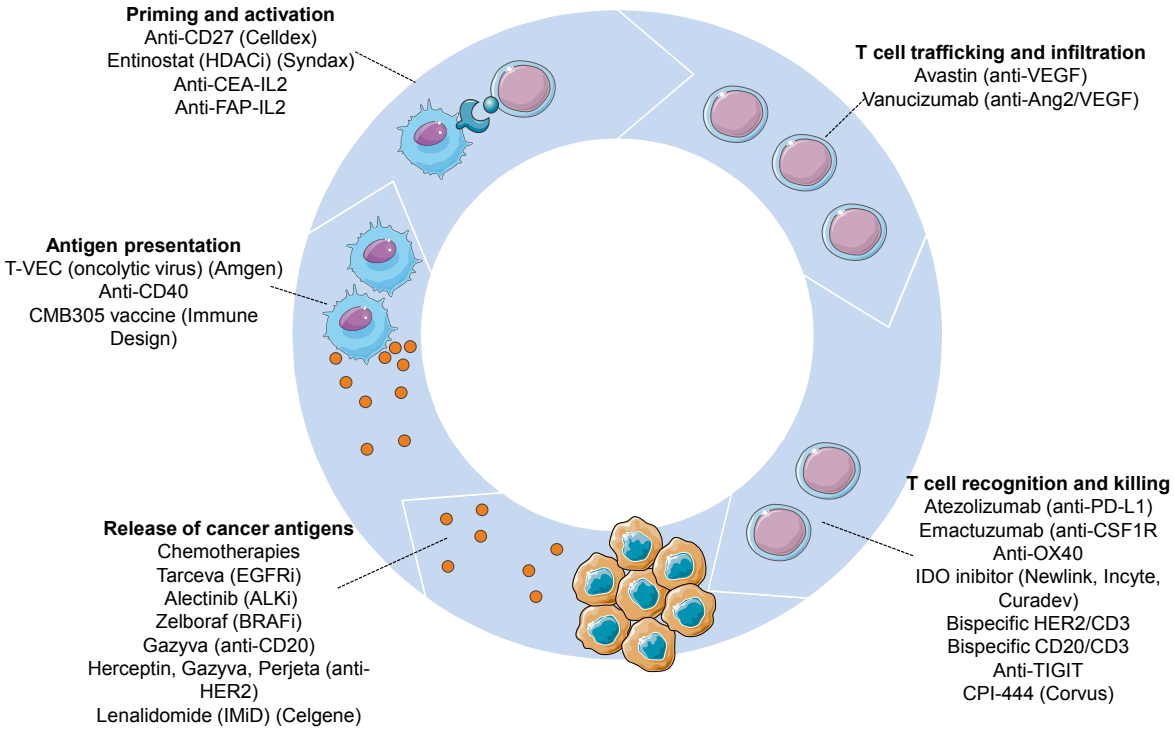
In our view, the development portfolios of these three groups are fairly comprehensive and enable them to fully address a far wider market than that allowed by cell therapies (note that solid tumours still remain a figment of the imagination for these therapies). As such, it is likely that they above all prefer to focus on approaches with a far larger and more tangible potential in the short term, and in view of recent transaction multiples, this is understandable. In other words, we think that these three big pharma groups will only take interest when 1) CAR-T potential in solid tumours is more proven (and this would probably be thanks to new designs), 2) allogeneic approaches have been validated (especially that of Cellectis).

**Fig. 43: BMS –focus areas in immuno-oncology**




*Source: Adapted from BMS, JPM Healthcare conference (Jan. 2016)*

**Fig. 44: Roche – oncology portfolio**




*Source: Adapted from Roche FY 15 results presentation; Bryan, Garnier & Co, ests.*

- **Sanofi**

Cellectis' CAR-T would help Sanofi make up some of the time lost in immune-oncology

Sanofi is a slightly more specific case. For many years, oncology has not really been part of its priority therapeutic segments (contrary to diabetes, animal health and vaccines). However, the recent arrival of Olivier Brandicourt seems to have resulted in a change of direction. A few months ago, the company indeed announced a new deal with Regeneron in the immune-oncology field, with the idea being to develop a PD-1 inhibitor baptised REGN2810 and currently in Phase I, as well as other molecules with fairly well-known targets (LAG3, GITR, etc.). A short time afterwards, an agreement was signed with Innate Pharma in order to jointly develop bispecific antibodies (but no target was unveiled).

However, Sanofi's pipeline is still far from matching that of other major laboratories in the field (and is also less well advanced). Given the speed with which rivals are developing their pipelines, it is clear that other licencing deals will have to be made during coming months, if they really want to make up for lost time. **Assuming that Sanofi is indeed interested in Cellectis' CAR-T cells, we believe that it would focus especially on UCART38** for all the reasons we have already mentioned, but also because the development of isatuximab has enabled it to acquire fairly comprehensive knowledge of CD38 and myeloma.

# 10. Calyxt: a forgotten but promising asset

Cellectis also has a subsidiary specialised in agro-biotechnology, Calyxt. This 100%-owned subsidiary clearly stands out from other companies in the market and we believe it should be also be a significant value creator in coming years.

- **What value added for Calyxt?**

Modified farm products but 1) not GMO and 2) faster to develop

Modifying certain characteristics of farm products is nothing new in itself. However, the fact that Calyxt only eliminates a few endogenous genes has a strong implication from a regulatory stance: the ensuing products are not considered as genetically modified organisms (GMO) by the various relevant authorities. In concrete terms, this should enable the company to 1) develop lower cost projects (less than USD10m vs. USD150-200m for a classic GMO like Monsanto's), 2) follow a less tortuous and shorter regulatory path (six years theoretically rather than 15), and 3) penetrate countries that are fairly against these approaches (especially Europe) more easily on the commercial front.

Several products are currently being developed, but two of them are fairly close to marketing (2018e).

**Fig. 45: Calyxt development pipeline**

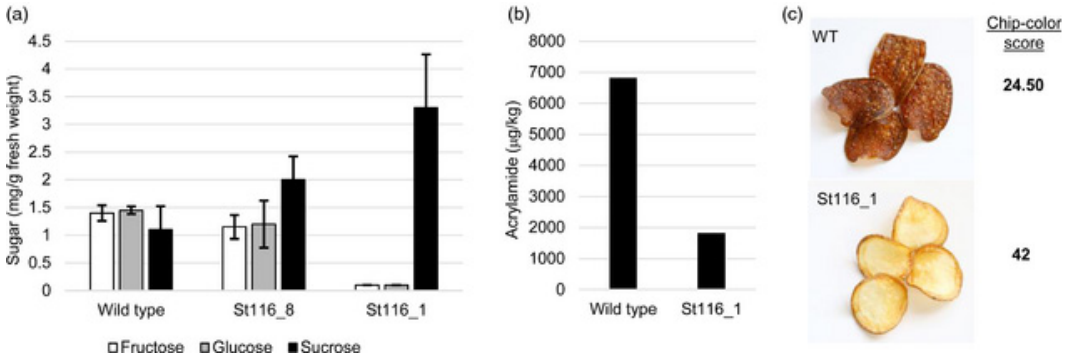
| Product | Trait | Discovery | Estimated field trial | First commercial launch |
|---|---|---|---|---|
| Soybean | No trans fat | Done | 2015 | 2018 |
| | Low linolenic oil | Done | 2016 | 2019 |
| | Low transfat/low linolenic oil stack | Done | 2017 | nd |
| | Protein content | Ongoing | 2017 | nd |
| | Herbicide resistance | Ongoing | 2017 | nd |
| | Improved yield | Ongoing | 2017 | nd |
| | Drought tolerance | Ongoing | 2017 | nd |
| Potato | Cold storage | Done | 2015 | 2019 |
| | Browning reduction | Done | 2016 | nd |
| | Cold storage/browning reduction stack (fries variety) | Ongoing | 2018 | nd |
| | Cold storage/browning reduction stack (chips variety) | Ongoing | 2018 | nd |
| | Late blight and virus resistance | Ongoing | 2019 | Nd |
| Canola | Improved oil | Ongoing | 2017 | nd |
| | Nitrogen us efficiency | Ongoing | 2018 | nd |
| Wheat | Low gluten | Ongoing | 2016 | 2022 |
| | Improved starch | Done | 2017 | nd |
| | Disease resistance | Done | 2016 | nd |
| Corn | High lysine/tryptophan | Ongoing | 2020 | nd |
| | Improved yield | Ongoing | 2020 | nd |

*Source: Company Data; Bryan, Garnier & Co ests.*

■ **A potato that can be stored in a refrigerator**

Calyxt' first candidate is a potato that can be stored in a refrigerator without acrylamide (an element known for its neurotoxic and cancerous properties) being generated when it is fried and without its taste and colour being affected following an increase in the sugar content. A potato with these characteristics is interesting from an industrial perspective since germination can be better controlled (to limit it as far as possible, the temperature should be kept below 4°C) and there is no need for germination inhibitors etc.

**Fig. 46: Modified potato – sugar and acrylamide levels after refrigeration**




*Source: Clasen et al, Plant Biotechnology Journal 2015*

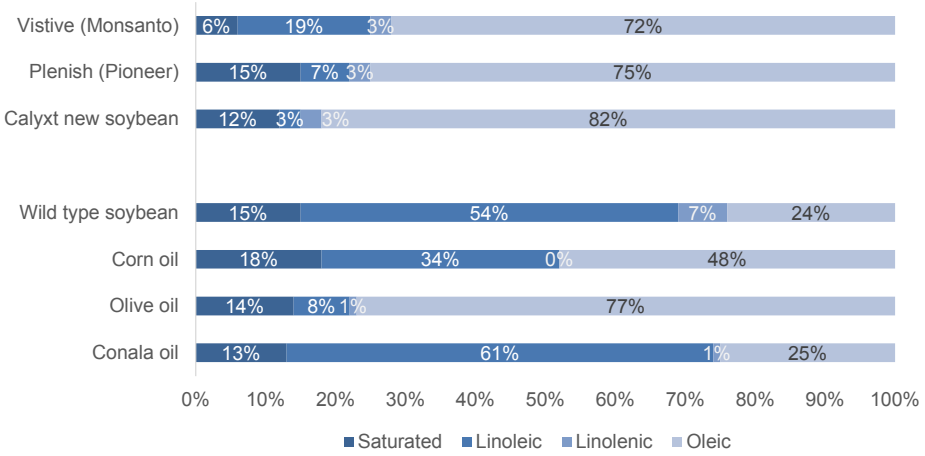
Note that several other versions are likely to be developed over coming years. In addition to this possibility of being stored at low temperatures, the company hopes to add the possibility of reducing browning after cooking (following caramelisation of sugar).

■ **Soya oil with lower (trans) fat**

A soya oil with the lowest transfat content just as regulations impose a drastic cut in their use…

The second project is a soybean that yields an oil with a low transfat content (linoleic and linolenic acids in particular), with the aim of reducing cardiovascular risk. However, beyond considerations specific to this candidate, note that 1) the FDA recently requested a drastic reduction in artificial transfats in the make-up of food products and 2) industrialists only have three years to comply with this new regulation. The timing is perfect for the oil obtained from Calyxt's soybean, especially since the concentration of linoleic and linolenic acids seems to be lower not only than that of classic soya oil, but also relative to its direct rivals: Monsanto's Visitive Gold and Pioneer's Plenish (see Fig. 47).

**Fig. 47: Characteristics of Calyxt soya vs rivals**




*Source: Company Data; Bryan, Garnier & Co ests.*

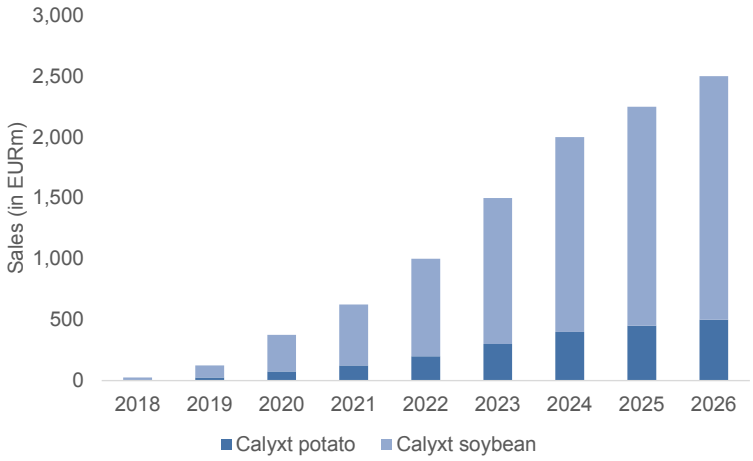
- **Potential sales of EUR2.5bn**

In view of the various advantages provided by Calyxt's technology, we are more than convinced that the major sector industrialists have already taken huge interest (Monsanto, DuPont Pioneer and Syngenta to mention only these). While the company has preferred to remain independent so far, we believe it has every interest in creating marketing agreements with these groups. This is the assumption we have factored into our model, since we estimate that sales would be far more optimal if they were generated with a player with sufficient cultivatable land, and with the ability to offer a bundle pack.

The global potato market is worth some USD30bn, for production of 370m tonnes. It would appear that the US accounts for around 10% of this and the share of emerging markets has already exceeded that of western markets since 2005. In addition, some 30-50% of this production is destined for chips and crisps manufacturing. Given that there are no real rivals in this market, we believe that sales of USD500m are feasible and we would also say that this is a somewhat cautious figure.

Meanwhile, the soybean market is thought to be worth USD40bn. The competitive backdrop is slightly denser with Monsanto and DuPont Pioneer already marketing genetically modified soya. However, the potential status of best-in-class non-OGM for Cellectis' soya gives reason for optimism and as such, we expect peak sales of EUR2.5bn, based on a prospective market share of 5%e.

**Fig. 48: Calyxt – sales forecasts (2018-2026e)**




*Source: Bryan, Garnier & Co ests.*

# 11. Valuation

## 11.1. Initiation at Buy with a FV of EUR37

**We are initiating coverage of the stock with a Buy recommendation and Fair Value of EUR37.** As always, our valuation is derived from a sum-of-the-parts (SOTP) calculation with each drug candidate valued in its target indications via a DCF model. In all cases, we have modelled our FCF on the basis of a 12.0% discount rate and over an explicit period running from 2016 to 2030, before applying a probability of success rate depending on the stage of the project's clinical progress.

**Fig. 49: BG valuation**

| Drug candidates | Indications | Clinical stage | WACC (%) | NPV (EURm) | PoS (%) | r-NPV (EURm) | Per share (EUR) |
|---|---|---|---|---|---|---|---|
| UCART19 | Acute Lymphoblastic Leukemia (ALL) | Phase I | 12.0% | 101.6 | 35% | 35.5 | 1.0 |
| UCART19 | Chronic Lymphocytic Leukemia (CLL) | Phase I | 12.0% | 174.4 | 35% | 61.1 | 1.7 |
| UCART19 | Non-Hodgkin Lymphomas (NHL) | Phase I | 12.0% | 216.1 | 35% | 75.6 | 2.1 |
| UCART123 | Acute Myeloid Leukemia (AML) | Phase I | 12.0% | 198.5 | 20% | 39.7 | 1.1 |
| UCART38 | Multiple Myeloma (MM) | Phase I | 12.0% | 572.7 | 35% | 200.4 | 5.7 |
| UCART38 | Non-Hodgkin Lymphomas (NHL) | Phase I | 12.0% | 186.7 | 35% | 65.4 | 1.9 |
| UCARTCS1 | Multiple Myeloma (MM) | Phase I | 12.0% | 383.2 | 35% | 134.1 | 3.8 |
| Calyxt | Agribusiness | Phase I | 14.0% | 2,065.0 | 20% | 413.0 | 11.7 |
| **= Enterprise Value** | | | | **3,898.1** | **26%** | **1,024.8** | **29.1** |
| (+) Net cash | | | | 284.0 | 100% | 284.0 | 8.1 |
| **= Equity Value** | | | | **4,182.1** | **31%** | **1,308.8** | **37.2** |

*Source: Bryan, Garnier & Co ests.*

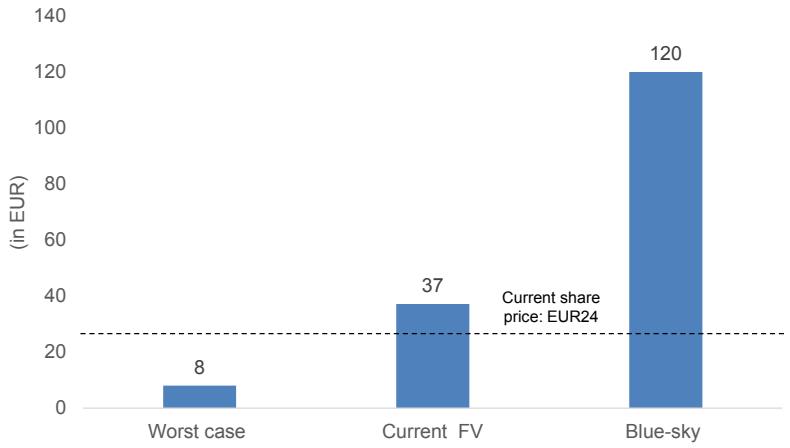
We have assumed higher probability of success ratios than we might apply under another framework. Although the various projects are primarily in phase I trials, we would note that all of the targets have been validated with other CAR-Ts or with therapies redirecting T cells, and that the very principle of CAR T-cells should also be ratified with the announcement of the first marketing approvals this year. Note however, that we have made a slight exception for UCART123 in that the validity of CD123 as a therapeutic target is far less well established.

## 11.2. A FV of EUR120 in a faultless scenario

As our readers know, it is important to provide valuations depending on various scenarios, whether negative or positive. In the case of Cellectis, we believe it is important to consider what the company's potential could be in the case of a clinical success or several successes.

At the current share price, our FV points to upside potential of almost 60% (whereas we are positioned at the low end of the consensus). Note however, that our FV in a faultless scenario could be multiplied by 5 pointing to a figure of EUR120 whereas cash represents EUR8 per share (or downside of 65% in a worst-case scenario). In short, the share's risk-reward profile looks pretty attractive.

**Fig. 50: BG valuation**




*Source: Bryan, Garnier & Co ests.*

Some observers could nevertheless point out that there are too few catalysts underpinning our investment case apart from the DSMB analysis. This is eventually true if we limit ourselves to Cellectis' communication. However, we believe we should extend our analysis to the sector in general. In this respect, we believe 2016 should be a year rich in news. Although the exact timing has not been given, CTL019 could be the first CAR-T anti-CD19 to be approved, in paediatric ALL. A cross-reading would clearly be positive, especially if labels are not overly restrictive. Finally, it is not impossible that other laboratories communicate on the feasibility and efficacy of their CAR-Ts in solid tumours.

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For the purposes of this Report, the Bryan Garnier stock rating system is defined as follows:

**Stock rating**

BUY — Positive opinion for a stock where we expect a favourable performance in absolute terms over a period of 6 months from the publication of a recommendation. This opinion is based not only on the FV (the potential upside based on valuation), but also takes into account a number of elements that could include a SWOT analysis, momentum, technical aspects or the sector backdrop. Every subsequent published update on the stock will feature an introduction outlining the key reasons behind the opinion.

NEUTRAL — Opinion recommending not to trade in a stock short-term, neither as a BUYER or a SELLER, due to a specific set of factors. This view is intended to be temporary. It may reflect different situations, but in particular those where a fair value shows no significant potential or where an upcoming binary event constitutes a high-risk that is difficult to quantify. Every subsequent published update on the stock will feature an introduction outlining the key reasons behind the opinion.

SELL — Negative opinion for a stock where we expect an unfavourable performance in absolute terms over a period of 6 months from the publication of a recommendation. This opinion is based not only on the FV (the potential downside based on valuation), but also takes into account a number of elements that could include a SWOT analysis, momentum, technical aspects or the sector backdrop. Every subsequent published update on the stock will feature an introduction outlining the key reasons behind the opinion.

**Distribution of stock ratings**

BUY ratings 63.4% NEUTRAL ratings 29.1% SELL ratings 7.5%

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Please see the section headed "Important information" on the back page of this report.

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