CAR-T for r/r CLL – the next logical step?

LONDON, UK----19th October 2017----ExpertREACT. r/r-CLL is a logical target for the manufacturers of CAR-T cell therapies. However, with treatment advances in small molecule inhibitors and checkpoint mAbs, product positioning seems less obvious than ALL and NHL (DLBCL).

Chronic lymphocytic leukemia (CLL) is the most common form of leukemia in the Western world representing ~1% of all new cancer cases in the US and UK. The disease is characterised by lymphocyte accumulation in blood, bone marrow, lymphatic tissues, liver and spleen. During CLL, apoptosis of lymphocyte clonal cells is impaired due to genomic aberrations which lead to bone marrow failure, anaemia, thrombocytopenia and susceptibility to infections. Although CLL can occur in both B- and T-lymphocyte forms, >95% of patients express the B-lymphocyte form of the disease.

Worldwide incidence of leukemia in 2012 was 351,965 cases (GLOBOCAN) with an age standardised rate of 4.7 per 100,000 (1). Figures for CLL are not provided but previous studies have shown it to constitute ~1/3 of total number of leukemia cases in Western countries (2). According to SEER (3), in 2017 the US recorded ~20,000 diagnosed cases (ASR of 4.4 per 100,000) and ~4,600 deaths. An estimated 130,965 people in the US live with or are in remission from CLL. The median age of CLL diagnosis is ~70 years, with around a quarter of patients <65 years. The disease is more predominant in males than females.

CLL patients are diagnosed at various stages of disease progression and fall into either symptomatic (progressive disease requiring therapy) or asymptomatic (watchful waiting) categories. Most patients will progress to symptomatic disease and eventually relapse following first line treatment (~20% relapsing within 2 years (4)). Stem cell transplant can be curative, but is often limited by patient age, comorbidities, and the potential for graft vs host disease (GvHD).

The standard 'chemo-immunotherapy' approach for CLL involves nucleoside analogues, alkylating agents and monoclonal antibodies e.g. fludarabine, cyclophosphamide, and rituximab (FCR) or bendamustine and rituximab (BR). Recent improvements in therapy (for high risk and refractory/relapsed patients) include the use of B cell receptor signalling inhibitors such as **Ibrutinib** (Imbruvica®, AbbVie, Janssen) (a Bruton's Tyrosine Kinase (BTK) inhibitor) and Idelalisib (Zydelig®, Gilead) (a PI3K-isoform selective inhibitor) and the apoptosis regulation inhibitor **Venetoclax** (Venclexta®, Abbvie, Genentech Roche) (an inhibitor of B-cell lymphoma-2 (BCL-2)). These orally available agents together with cytogenetic screening are now shifting the definition of 'standard treatment' with durable responses (ORR of 83% and PFS of 63% (5) and a median progression free survival of 52 months (6). Patients with the high risk genetic aberration del(17p)/TP53mut now receive Ibrutinib with progressive disease rather than chemo-immunotherapy. Importantly, only 5-7% of previously untreated patients demonstrate del(17p), this figure is significantly higher in relapsed/refractory patients (30-50%) (6,7) making them a significant market segment for manufacturers.

Despite the high efficacy demonstrated with Ibrutinib in clinical trials, questions remain regarding its toxicity (long-term use), cost and resistance generation. For example, one study showed toxicity, resistance and disease progression to cause 50% of patients to permanently discontinue use (5). On balance, chemo-immunotherapy remains the gold standard treatment for lower risk CLL patients (8) with those in higher risk categories being treated with B-cell signaling inhibitors (9).

Novel treatments for CLL in the pipeline include monoclonal antibodies (anti-CD19, Morphosys; anti-CD370, Boehringer Ingelheim), and bispecific antibodies (anti-CD20/CD3, Genentech) which are being tested in various combinations with B-cell inhibitors (Ibrutinib, Idelasilib, Venetoclax) and existing monoclonal antibody (Obinutuzumab).

High expression of the checkpoint molecules PD-1 and CTLA-4 in T-cells from CLL patients compared to healthy donors T-cells also indicates that the application of the checkpoint inhibitors

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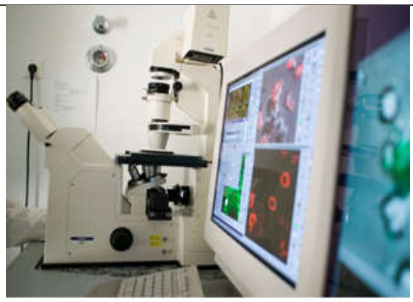
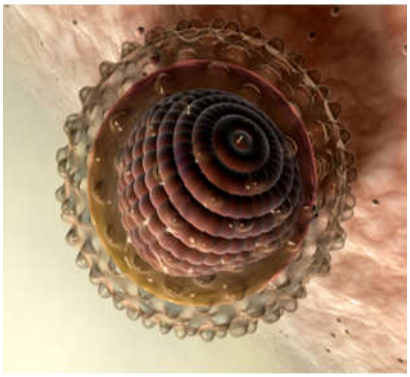




Nivolumab (Opdivo®, anti-PD1, BMS), **Pembrolizumab** (Keytruda®, anti-PD1, Merck), **Durvalumab** (Imfinzi®, anti-PD-L1, AstraZeneca) and **Ipilimumab** (Yervoy®, anti-CTLA-4, BMS) would have efficacy in CLL. Several trials including these combined with additional agents (e.g. Idelalisib, Ibrutinib, Lenalidomide, Rituximab, Obinutuzumab) are ongoing (10). Encouraging data has been presented with Nivolumab and Ibrutinib in patients with relapsed/refractory CLL or Richter's transformation (RT), or untreated patients with high-risk del(17p) CLL (11,12). In this small 13 patient study the overall response rate (ORR) was 80% for Ibrutinib plus Nivolumab in patients with relapsed/refractory CLL, and for patients with RT (5 in total), the ORR was 60% with two complete responses. Thus, the future utility of checkpoint inhibitor combination therapies in CLL remains a strong possibility.

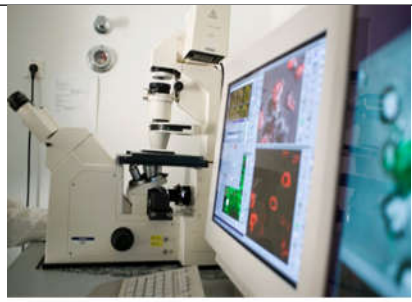
Chimeric Antigen Receptor T-cells (CAR-T) therapy might be a potential immunotherapy for CLL. CAR-T cells are *ex-vivo* genetically modified autologous T-cells expressing an antigen binding domain coupled with the intracellular signaling domain of a T-cell receptor together with co-stimulatory molecules. Therapy is usually performed in a specialized treatment facility and involves leukapheresis, the extraction of the patient's T-cells, their genetic modification and expansion, followed by reinfusion to the patient as a single treatment. The first FDA approval for a CAR-T therapy was granted in 2017 for **Kymriah® (CTL019, Tisagenlecleucel, Novartis)** for treating pediatric acute lymphoblastic lymphoma (B-ALL). Kymriah® has demonstrated huge excitement in the field by achieving a complete response rate of 83% together with minimal residual disease (MRD) –ve status in those patients during the global multicentre clinical trial ELIANA (13). A second approval for **Axi-Cel (KTE-C19) (Yescarta)** by Gilead/Kite Pharma has just been granted this month for non-Hodgkin's Lymphoma (NHL) following results of their ZUMA-1 trial showing an initial complete response rate of 54% (14) and long-term remission of up to 56 months in Diffuse Large B Cell Lymphoma (DLBCL) patients (15). Common adverse events with CAR-T cell therapy include cytokine release syndrome (CRS) and neurotoxicity (NT) which are managed with the IL-6R antagonist tocilizumab.

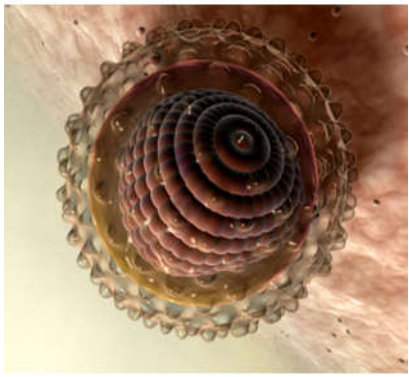
Novartis' and Kite Pharma's CAR-T therapies target the antigen CD19, the B-cell surface protein expressed during B-cell development and expressed on ALL, NHL and CLL malignant cells. Due to the success of these therapies in ALL and NHL so far, applying these to CLL seems to be the next logical step. Results from clinical trials have now been published on CD19 directed CAR-T cell therapy in CLL from the University of Pennsylvania Abramson Cancer Center (in collaboration with Novartis since 2012) on CTL019 (16,17,18,19). Overall responses were 53% in relapsed/refractory CLL patients with complete remission in 29% of patients treated at an optimal dose of $5x10^8$ cells (19). Furthermore, the same institution investigated the response of CTL019 in patients previously treated with Ibrutinib and found that these patients show improved *in vivo* and *ex vivo* T cell expansion of CTL019 (20) indicating synergy between the two therapies.

The Abramson Cancer Center has also initiated a clinical trial (March 2016) investigating a CAR-T directed towards the antigen Receptor Tyrosine Kinase-like Orphan receptor 1 (ROR1) in malignancies including CLL, ALL, breast carcinoma, NSCL cancer (21). ROR1 is highly expressed on B-cell CLL cells but not on normal B-cells and is thus also an attractive tumor specific target (22).

Novartis and Abramson Cancer Center are also developing a CAR-T cell therapy with humanized scFv domains (rather than murine regions of CTL019) called CTL119. This should improve targeting, persistence and efficacy of the CAR-T cells and potentially reduce any undesired host responses. A study of CTL119 in CLL patients in combination with Ibrutinib (23) is now also generating promising data (eight of nine patients with MDR-ve disease and CR at 6 months) (24, 25) and suggests a combination approach of these CAR-T cells with Ibrutinib for relapsed/refractory high-risk patients. Clinical studies at the Fred Hutchinson Cancer Research Center in collaboration with Juno Therapeutics and their CD19 directed CAR-T therapy JCAR014 has also reported promising data in CLL patients.

Juno Therapeutics has several CD19 targeting therapies in development, the most advanced of which is JCAR017 for DLBCL (granted Breakthrough Therapy designation by the FDA for treatment of relapsed/refractory aggressive large B cell NHL and PRIME designation by the EMA for treatment of relapsed/refractory DLBCL in December 2016 (26) for which they expect FDA approval in 2018 with JCAR014 following in 2019 for CLL (27,28)





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JCAR014 CLL patients who were previously treated with Ibrutinib showed an overall response rate of 74% with a CR rate of 21% with manageable toxicity (29) supporting the development of JCAR017 for CLL in second and third line CLL and in combination with Ibrutinib during 2017-18 (30). A further approach being investigated by Juno Therapeutics is the use of 'armoured' CAR-T cells where cells are also engineered to constitutively express the ligand 4-1BBL in order to enhance T cell proliferation, IL-2 secretion, survival and the cytolytic activity of the T cells (31,32) Although no data are reported to date, this approach is hoping to improve the responses of CAR-T cells in CLL (typically 20-45% in many studies compared to ALL where overall responses of 80-90% are found).

Gilead/Kite Pharma are also hoping to initiate a clinical study with Axi-Cel (KTE-C19) in CLL with patients expecting to be enrolled during 2017 (33).

For manufacturers of CAR-T treatments the CLL indication might appear an attractive commercial target beyond ALL and DLBCL. The number of newly diagnosed CLL cases is among the highest of the leukemias (20,100 new cases in the US in 2017 vs 5,970 for ALL) and unmet need remains high since r/r CLL patients have a poor prognosis. However, one key question is which patients would be eligible for CAR-T therapy since a significant proportion are asymptomatic (~74% (34)) and assigned 'watch and wait' until symptoms develop. Also, what will be the impact of the newly introduced small molecule inhibitors, Ibrutinib, Idelalisib and Venetoclax which have revolutionized the treatment of CLL? These are also used for refractory/relapsed patients (the same target for CAR-T in ALL & DLBCL). For **Venetoclax** (launched 2016), it's simply too early to assess any long-term treatment benefit. Overall, with the development of second generation B-cell signaling inhibitors and the possibility of combination approaches with checkpoint inhibitor monoclonal antibodies it is very difficult to predict an eventual position for CAR-T cell therapy.

Nevertheless, interest in the potential of CAR-T therapy for CLL remains. Price projections for Ibrutinib, Idelalisib and Venetoclax are predicted to cause a 590% increase in CLL management costs by 2025 with a cost of $604k per patient by that time (35,36) and stem cell therapy can cost up to $800k (37) Put in these contexts, CAR-T cell therapy (priced at $475k per treatment (38)) may seem like a favorable economic option if it can be a one-off approach.

CAR-T cell therapy is revolutionary in the treatment of hematological malignancies. Painstaking research has delivered a life-changing therapy for those with a previously poor prognosis in pediatric B-cell ALL, and now there is hope for NHL. The application of this therapy, either alone or in combination with existing agents to CLL seems to be a logical next move. However, for CAR-T manufacturers optimum product positioning seems far less straightforward.

References to this article are available on request.