



**POST-ASH** Issue 7, 2014

# **Anti-CD19 CAR T-Cell Therapy in Children with Relapsed/Refractory ALL**

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## CME INFORMATION

### OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Hematology (ASH) annual meeting, to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. As such, these events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unprecedented and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they're aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because they are not only confronted almost overnight with thousands of new presentations and data sets to consider but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on chimeric antigen receptor T-cell therapy for leukemia and lymphoma from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists, hematology-oncology fellows and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

### LEARNING OBJECTIVES

- Develop an understanding of the mechanism of action of chimeric antigen receptor T-cell therapy, and evaluate the emerging efficacy and safety data with this therapeutic approach under evaluation in the front-line and relapsed/refractory settings for B-cell lymphoma and leukemias.
- Evaluate the benefits and risks of the addition of gemtuzumab ozogamicin to standard chemotherapy and of other emerging agents such as novel FLT3 inhibitors or hypomethylating agents for the treatment of acute myeloid leukemia.

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**FACULTY** — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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No real or apparent conflicts of interest to disclose.

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Hardware/Software Requirements:

A high-speed Internet connection

A monitor set to 1280 x 1024 pixels or more

Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later

Adobe Flash Player 10.2 plug-in or later

Adobe Acrobat Reader

(Optional) Sound card and speakers for audio

Last review date: May 2014

Expiration date: May 2015

To go directly to slides and commentary for this issue, [click here](#).

On this final issue of our review of select key papers presented at the American Society of Hematology annual meeting, we focus on a handful of fascinating early clinical reports on CART and a smattering of what's new in AML.

### **CART clinical trial data**

Although we heard about the seemingly miraculous effects of this novel therapeutic approach in 2012 in Atlanta, New Orleans was the true coming out party for CART-based approaches, specifically those targeting CD19. Led by the powerhouse team at the University of Pennsylvania, which includes Dr David Porter, we were treated to numerous fascinating presentations that have generated great excitement and enthusiasm.



**David L Porter, MD**

Since ASH I have been fortunate enough to interview Dr Porter on 2 occasions ([click for audio](#)), and it is impossible to hear about this dramatic story without getting goose bumps.

The concept behind Penn's CART-based approach is intriguing. Patients undergo leukapheresis, after which their T-cells are transduced with a lentivirus encoding an anti-CD19 single-chain variable fragment linked to 4-1BB and CD3- $\zeta$  signaling domains. The genetically modified cells are then expanded ex vivo, and soon after a course of lymphocyte-depleting chemotherapy they are then reinfused into the patient where, as documented previously and in new reports at ASH, they expand (up to 10,000-fold), persist functionally (beyond 3 years) and exert a direct antitumor effect.

Early efforts by the group have focused on very advanced chronic lymphocytic leukemia (CLL) and B-cell acute lymphoblastic leukemia (ALL), and although they hoped to see some discernible benefit in early testing, as related by Dr Porter, the initial clinical responses were stunning in rapidity and depth. Much of this work was updated and expanded on in New Orleans. Dr Stephan Grupp [presented longer follow-up outcomes](#) from 17 adults and children with relapsed/refractory ALL revealing that 82% achieved a complete response (CR). Similarly, Dr Porter [provided an update](#) from their Phase I study in which 8 of 14 patients with extensively pretreated CLL had objective responses, including 4 patients with CRs, none of whom have yet experienced

relapse. He also unveiled data from their dose-finding randomized Phase II study demonstrating that 7 of 18 patients responded, including 3 CRs, with no correlation between dose and outcome or toxicity.

Perhaps the highlight of these presentations, at least in my mind, was an impressive set of scans that Dr Porter displayed from a patient with del(17p) CLL treated on their original pilot study. Amazingly, 3 months after receiving the CART infusion this individual, whose disease had progressed through 10 prior therapies, including ibrutinib and radiation therapy, was pretty much disease free in peripheral blood and bone marrow.

In discussing this work with Dr Porter, I was eager to learn more about the profound and rapid tumor lysis/cytokine release syndrome (CRS) that has been described with this therapy. I was wide-eyed as he detailed the team's early experiences with this scary complication that generally occurred within the first few weeks of treatment at the peak of initial T-cell expansion and initially led to life-threatening multiorgan failure. What was perhaps most compelling was that the team was able to quickly determine that the key cytokine causing this syndrome was IL-6, and they were able to successfully intervene with a novel IL-6 receptor antibody approved for rheumatoid arthritis (tocilizumab).

Penn is not alone at the forefront of this research, and at ASH the Memorial group also reported activity with a slightly different anti-CD19 CAR platform across several diseases. In high-risk CLL, Dr Jae Park **presented preliminary data** from a Phase I study evaluating this approach as consolidation after up-front rituximab-chemotherapy. While the data set was quite small — 8 patients with 2 CRs and 2 partial responses — it provides an important proof of principal that ultimately may allow some patients with CLL to receive a short-term treatment that will lead to prolonged tumor control. Relevantly, the study results suggest greater benefit in patients with lower tumor burden, and Dr Porter believes that an important future strategy will be initial cytoreduction, particularly with novel B-cell inhibitors like ibrutinib, followed by an attempt at cure with CART.

Memorial's Dr Marco Davila **also reported** on CAR therapy as a bridge to allotransplant in patients with B-cell ALL, including those with Philadelphia chromosome-positive disease. Importantly, responses were rapid, occurring as early as 7 to 14 days, CRS was manageable and 10 of 12 patients with detectable disease before CAR therapy became minimal residual disease-negative. Four patients went on to allotransplant with 5 more being prepped for it.

The NCI, too, is very involved in this field, and at ASH they provided us with more data on the **use of this technology in ALL** as well as our **first look at it in B-cell lymphomas**, where 5 of 8 patients with chemotherapy-refractory diffuse large B-cell lymphoma or primary mediastinal B-cell lymphoma experienced objective tumor responses.

The next step for this fascinating and innovative treatment strategy is to not only obtain more data but also to investigate the feasibility and reproducibility of doing this on a larger-scale basis.

## AML: Life beyond 3 plus 7

The dismal current landscape of this important cause of mortality is reflected by the fact that the only compound approved for this disease in the last 20 years, gemtuzumab ozogamicin (GO), was removed from the market by the FDA 4 years ago due to toxicity concerns.

As such, for far too long conversations about AML management have revolved around optimal induction and consolidation chemotherapy doses and schedules and the role for various transplant strategies. However, the rapidly emerging translational and related clinical science that permeates ongoing AML research has many optimistic that brighter days are ahead ([click for summary slides of studies discussed below](#)).

One of the more talked about areas is management of the 30% of patients with FMS-like tyrosine kinase 3 (FLT3) mutations, and in the Big Easy Dr Jorge Cortes presented a provocative study on the effects of the as yet unapproved FLT3 inhibitor quizartinib. One of the proposed benefits of this agent is that it is more specific for the target than tyrosine kinase inhibitors such as sorafenib, which is sometimes employed off label when no other alternatives exist. In this Phase II study using lower doses of quizartinib in 76 patients, a 47% CR rate with acceptable toxicities was reported. All eyes are on the ongoing Phase III study evaluating this compound in hopes that it may end up as a useful tool in practice.

The MD Anderson group also reported on SGI-110 — a novel molecule that combines decitabine with guanosine to produce a longer half-life and potentially higher areas under the curve than decitabine. Importantly, in this Phase II study this subcutaneously administered hypomethylating agent resulted in an encouraging preliminary objective response rate of 53% in elderly patients with treatment-naïve AML. Dr Hagop Kantarjian and his group at MD Anderson are interested in doing a study comparing this agent to conventional decitabine or azacitidine.

Because activating KIT mutations are present in 25% to 30% of patients with core binding factor (CBF) AML, it has been hypothesized that KIT inhibition might provide therapeutic benefit. In this regard, the CALGB reported on a single-arm trial evaluating the addition of dasatinib to induction chemotherapy in patients with molecular confirmation of CBF AML. Reported at ASH, the trial resulted in an encouraging CR rate of 92% in 59 evaluable patients, but many are reserving judgment about this approach until further follow-up is available.

Given its activity in a multitude of hematologic cancers, it should probably come as no surprise that lenalidomide is also being evaluated in AML. Significantly, preliminary results look encouraging with a CR rate of 43% in 37 elderly patients over age 70 with low-dose lenalidomide added to low-dose Ara-C (LDAC). Perhaps even more importantly, a 5-gene molecular signature has been identified that appears highly predictive of treatment response with 87% overall accuracy.

Additionally, although the previously mentioned anti-CD33 antibody-drug conjugate GO is no longer available, at ASH we saw data reinforcing its evidence-based benefit most

specifically for patients with CBF AML. Described in [a meta-analysis, a pediatric study and a longitudinal analysis](#) of trials of the UK MRC/NCRI group, these results all point to a modest advantage with limited toxicity. Whether GO will make it back into the clinic, however, remains unclear.

Finally, in terms of the FDA and AML, one of the more interesting and positive recent developments from the agency has been the 2012 implementation of the “Breakthrough Therapy” designation pathway, which fast-tracks promising agents in diseases with important unmet needs. Over the past year on our CME programs we have discussed many exciting oncology compounds that have earned this designation, and just 2 weeks ago we saw this novel pathway in action as the second-generation ALK inhibitor ceritinib was granted accelerated approval in ALK-positive non-small cell lung cancer based on the results of a single-arm, open-label clinical trial enrolling 163 patients.

Last fall, the selective and potent polo-like kinase (PLK) inhibitor volasertib became the only “AML drug” to join this short “Breakthrough” list. Volasertib inhibits PLK1 — the best characterized of the 5 known human PLKs and a critical enzyme regulating mitosis — resulting in cell cycle arrest and ultimately cell death (apoptosis). At ASH 2012 a randomized Phase I/II trial reported an impressive response rate advantage when the agent was added to LDAC in patients not eligible for intensive induction. These encouraging results led to the ongoing Phase III POLO-AML-2 trial with a similar randomization in patients age 65 or older with previously untreated AML not eligible for intensive induction. Although the future of this interesting agent is unclear, it seems plausible that in the next few years AML will join the other myeloid cancers in seeing the documented benefit of important new and clinically useful treatment strategies based on the evolution of understanding the underlying disease biology.

This concludes our ASH review series. If you’re heading to Chicago this month, join us at the end of each day for a series of evening symposia as we review what’s happening in [lung cancer](#), [gastrointestinal cancers](#), [non-Hodgkin lymphoma/multiple myeloma](#) and [HER2-positive breast cancer](#).

Neil Love, MD

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Miami, Florida

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# Anti-CD19 CAR T-Cell Therapy in Children with Relapsed/Refractory ALL

## Presentation discussed in this issue

Lee DL et al. **Anti-CD19 chimeric antigen receptor (CAR) T cells produce complete responses with acceptable toxicity but without chronic B-cell aplasia in children with relapsed or refractory acute lymphoblastic leukemia (ALL) even after allogeneic hematopoietic stem cell transplantation (HSCT).** *Proc ASH 2013*; **Abstract 68**.

Slides from a presentation at ASH 2013 and transcribed comments from a recent interview with David L Porter, MD (3/3/14)

**Anti-CD19 Chimeric Antigen Receptor (CAR) T Cells Produce Complete Responses with Acceptable Toxicity but without Chronic B-Cell Aplasia in Children with Relapsed or Refractory Acute Lymphoblastic Leukemia (ALL) Even After Allogeneic Hematopoietic Stem Cell Transplantation (HSCT)**

**Lee DW III et al.**

*Proc ASH 2013*; Abstract 68.

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# Background

- Survival with relapsed/refractory pediatric pre-B-cell ALL and non-Hodgkin lymphoma (NHL) is poor despite intensive chemotherapy and HSCT.
- CAR T cells combine the specificity and major histocompatibility complex independence of antibodies with the cytotoxic capacity of T cells.
- Through genetic engineering of T cells with a CAR that links a single-chain variable fragment for CD19, present on most NHL and ALL blasts, cytotoxicity can be specifically and fully activated with a single interaction.
- **Study objective:** To determine the efficacy and safety of anti-CD19 CAR T cells in pediatric patients with relapsed/refractory ALL and NHL.

Lee DW III et al. *Proc ASH* 2013;Abstract 68.

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## Ongoing Phase I Trial Design

### NCT01593696

#### Target accrual (n = 48)

Relapsed/refractory B-cell NHL or ALL  
Age 1-30 years  
CD19 positivity  
Ineligible or refused allogeneic stem cell transplant (SCT)

→ **Anti-CD19 CAR T cells**

#### Endpoints include:

- Feasibility of generating adequate numbers of CAR T cells from a population of patients at high risk, including after HSCT
- Response rate
- CAR T cell persistence and trafficking to extramedullary sites
- Safety

Lee DW III et al. *Proc ASH* 2013;Abstract 68; [www.clinicaltrials.gov](http://www.clinicaltrials.gov). Accessed April 2014.

## Study Methods

- Peripheral blood mononuclear cells were collected from patients by apheresis and immediately enriched for T cells using activating anti-CD3/CD28 beads.
- These cells underwent retroviral transduction of the CAR gene.
- After an 11-day process, patients who had received fludarabine (25 mg/m<sup>2</sup>/day on days -4, -3, -2) and cyclophosphamide (900 mg/m<sup>2</sup>/day on day -2) received a fresh infusion of CAR T cells.
- At data cutoff, 8 patients were enrolled and had received treatment.

Lee DW III et al. *Proc ASH* 2013;Abstract 68 (abstract only).

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## Patient Characteristics

Characteristic	n = 8
Age range	10-23 years
ALL	7 (87.5%)
NHL	1 (12.5%)
Pre-HSCT	4 (50%)
Post-HSCT	4 (50%)
With successful expansion of CAR T cells meeting the assigned dose level (transduction efficiencies of 18%-87%)	6 (75%)
Insufficient expansion to meet target dose	2 (25%)*

\* These patients received 3% and 14% of the target dose.

Lee DW III et al. *Proc ASH* 2013;Abstract 68 (abstract only).

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## Response Rates

	<b>n = 8</b>
Complete response (CR)	5/8 (62.5%)
ALL	5/7 (71.4%)
NHL	0/1 (0%)
Minimal residual disease (MRD)-negative CR	3/8 (37.5%)
ALL	3/7 (42.9%)*
NHL	0/1 (0%)

\* Includes 1 patient with primarily refractory disease to chemotherapy who proceeded to HSCT after CD19 CAR therapy

- Both patients who received cells below the target dose experienced antileukemia effects:
  - One experienced a transient CR
  - One experienced MRD-negative CR

Lee DW III et al. *Proc ASH* 2013;Abstract 68 (abstract only).

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## CAR T-Cell Expansion, Persistence and Trafficking

- CAR T cells have been identified in blood (0.1%-38%) and bone marrow (0.1%-5%) in all responding patients.
- CAR T cells have been found in:
  - Cerebrospinal fluid (CSF) of 3 patients (0.3%-17%)
  - Pleural fluid (13%) of a patient with NHL with pre-existing malignant pleural effusions
- CAR T cells are suspected to have caused Grade 1 scrotal edema in a patient with a remote history of testicular disease.
- One patient with CNS2 disease (<5 white blood cells/uL in the CSF and cytospin-positive for blasts) at the time of enrollment cleared all CSF blasts without additional intrathecal chemotherapy after CAR T cells were administered (max: 17% CAR T cells in CSF).
- The mean time to undetectable CAR T cells in any tissue in responding patients was 55 days.

Lee DW III et al. *Proc ASH* 2013;Abstract 68 (abstract only).

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## Treatment-Related Adverse Events

- Treatment was well tolerated.
- Two patients had Grade 2 cytokine release syndrome (CRS): Grade 3 fever, Grade 2 hypotension
  - These toxic effects resolved with IV fluids and correlated with high IL-6, GM-CSF, IFN $\gamma$ , TNF $\alpha$  and C-reactive protein.
- One dose-limiting toxicity (Grade 4 CRS) occurred and required vasopressors for hypotension.
- After identification of high plasma IL-6, the anti-IL-6 receptor antibody tocilizumab was administered and quickly reversed most toxicity from CRS.

Lee DW III et al. *Proc ASH* 2013;Abstract 68 (abstract only).

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## Treatment-Related Adverse Events (Continued)

- At the time of day 28 restaging, CD19-positive hematogones were detected in 4 of 5 patients with responsive disease (mean 81.4% of all CD19-positive cells).
  - This indicates that significant antileukemic effects can be induced by CD19 CAR T cells without chronic depletion of B-cell precursors.
- None of the patients with prior HSCT developed graft-versus-host disease despite the administration of donor-derived activated T cells harvested from the recipient.

Lee DW III et al. *Proc ASH* 2013;Abstract 68 (abstract only).

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## Author Conclusions

- Anti-CD19-CD28-zeta CAR T cells that mediate potent antileukemic effects can be reliably generated, even from patients with advanced disease with or without a history of allogeneic HSCT.
- Using intent-to-treat reporting, CR rates are high (62.5%) in this population of patients with refractory disease.
- CD19 CAR T cells traffic to extramedullary sites and can mediate antitumor effects in the CSF.
- Acute toxicity is manageable, and because the anti-CD19-CD28-zeta CAR T cells do not persist at high levels for prolonged periods, rapid resumption of B-cell lymphopoiesis occurs after therapy.

Lee DW III et al. *Proc ASH* 2013;Abstract 68 (abstract only).

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### **Investigator Commentary: Ongoing Phase I Study of Anti-CD19 CAR T Cells in Pediatric Patients with Relapsed/Refractory NHL or ALL**

This study focuses on a small number of patients with NHL or ALL treated with anti-CD19 CAR T cells. The results show remarkable complete remission rates — 5 out of 7 patients with ALL achieved a CR. Also, the study showed that this treatment strategy can be effective after allogeneic SCT. A unique and interesting finding from this study is that the modified CAR T cells were found in other compartments of the body. In 3 patients, the genetically modified cells were found in the CSF, and the cells were even found in the pleural fluid in 1 patient with NHL who had preexisting malignant pleural effusions.

This study describes a patient with active CNS2 disease and leukemia at the time of enrollment that were effectively eradicated by the CAR T cells. So the fact that these cells have the potential to traffic beyond the blood — into the bone marrow, CSF and pleural fluid — is remarkable. This suggests that it may also be possible to treat extramedullary disease with these cells and, in particular, leukemic meningitis, which is extremely complicated and difficult to eradicate with more conventional therapies. These results are unique, exciting and promising.

***Interview with David L Porter, MD, March 3, 2014***