



**POST-ASH** Issue 7, 2014

# Phase I Trial of CD19-Targeted CAR-Modified T Cells as Consolidation for Previously Untreated CLL

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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:

Hagop M Kantarjian, MD  
Chairman and Professor, Leukemia Department  
The University of Texas MD Anderson Cancer Center  
Houston, Texas

No real or apparent conflicts of interest to disclose.

David L Porter, MD  
Abramson Cancer Center  
University of Pennsylvania Health System  
Jodi Fisher Horowitz Professor of Leukemia Care Excellence  
Director, Blood and Marrow Transplantation  
Philadelphia, Pennsylvania

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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

[Research To Practice](#)

Miami, Florida

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# **Phase I Trial of CD19-Targeted CAR-Modified T Cells as Consolidation for Previously Untreated CLL**

## **Presentation discussed in this issue**

Park JH et al. **Phase I trial of autologous CD19-targeted CAR-modified T cells as consolidation after purine analog-based first-line therapy in patients with previously untreated CLL.** *Proc ASH 2013*; [Abstract 874](#).

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

## **Phase I Trial of Autologous CD19-Targeted CAR-Modified T Cells as Consolidation After Purine Analog-Based First-Line Therapy in Patients with Previously Untreated CLL**

**Park JH et al.**

*Proc ASH 2013*; Abstract 874.

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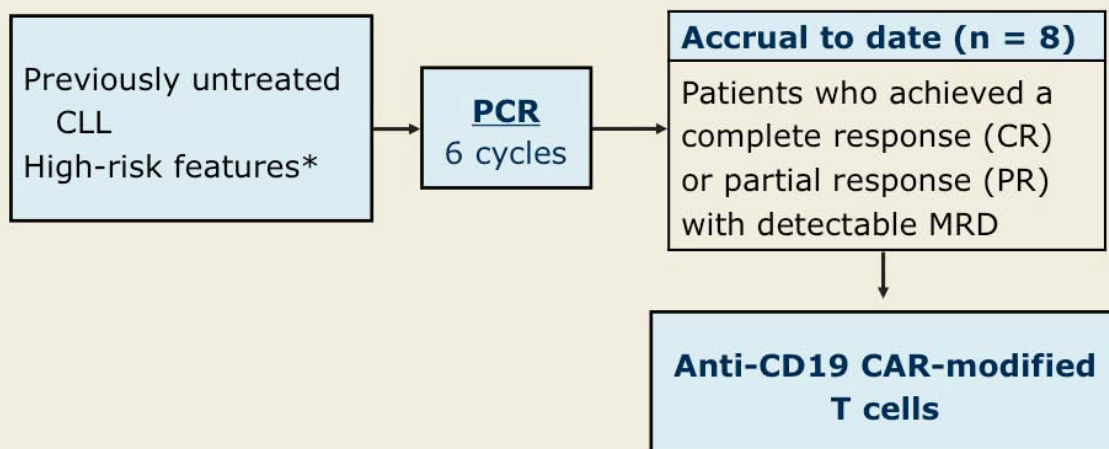
# Background

- T cells may be genetically modified to express chimeric antigen receptors (CARs) targeted to antigens expressed on tumor cells.
- Initial results from a Phase I trial in chemotherapy-refractory/relapsed CLL treated with autologous T cells modified to express CAR targeted to the CD19 antigen showed promise (*Blood* 2011;118:4817).
- Treatment with CD19-targeted CAR-modified T cells resulted in significantly increased rates of durable responses in CLL with reduced disease burden and chemotherapy-sensitive disease.
- **Study objective:** To determine the efficacy and safety of anti-CD19 CAR-modified T cells as consolidation therapy for patients with minimal residual disease (MRD) after first-line chemotherapy.

Park JH et al. *Proc ASH* 2013;Abstract 874.

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## Ongoing Phase I Trial Design



P = pentostatin; C = cyclophosphamide; R = rituximab

\* Defined by the presence of unmutated IgHV, del(11q) or del(17p)

Park JH et al. *Proc ASH* 2013;Abstract 874 (abstract only).

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## Study Methods

- Autologous T cells collected by leukapheresis were transduced with a retroviral vector encoding the anti-CD19 single-chain variable fragment linked to CD28 costimulatory and CD3zeta signaling domains.
- Patients received cyclophosphamide conditioning therapy followed 2 days later by the infusion of the CAR-modified T cells in 3 dose-escalating cohorts.
- Response assessment was performed according to the criteria established by the National Cancer Institute-sponsored working group.
- Serial bone marrow aspirate and blood samples were assessed for modified T-cell persistence.
  - This was assessed by flow cytometry, real-time polymerase chain reaction and cytokine profile analysis.

Park JH et al. *Proc ASH* 2013;Abstract 874 (abstract only).

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## Patient Characteristics

Characteristic	n = 8*
Median age (range)	61.5 years (45-68)
Unmutated IgHV	75%
Del(11q)	25%
Median follow-up from the time of T-cell infusion (range)	7 mo (2-12)
Median time from completion of up-front PCR chemotherapy to T-cell infusion (range)	6.5 mo (4-12)

\* To date, 8 patients have been enrolled

- 6 patients have received CAR-modified T cells, completing the 2 dose cohorts of  $3 \times 10^6$  and  $1 \times 10^7$  CAR-modified T cells/kg (3 in each cohort)

Park JH et al. *Proc ASH* 2013;Abstract 874 (abstract only).

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## Response Rates

- Patients who experienced a PR after first-line PCR chemotherapy and achieved a CR after T-cell infusion: n = 2
- Patients who achieved and maintained a PR: n = 2
- Patients with progressive disease (PD): n = 2
  - Of these 2 patients, 1 achieved a PR after 6 cycles of PCR but had progressive lymphocytosis with an absolute lymphocyte count doubling time of 1 month at the time of T-cell infusion.
  - The other patient experienced lymph node-only relapse while the bone marrow remained MRD-negative.

Park JH et al. *Proc ASH* 2013;Abstract 874 (abstract only).

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## Treatment-Related Adverse Events

- No dose-limiting toxicity was observed.
- Cytokine release syndrome (CRS), manifested by fever, nausea, anorexia and transient hypotension, was observed (n = 2).
  - None required treatment with steroids or other anti-inflammatory agents.
- There was a positive correlation between the development of CRS and modified T-cell persistence.

Park JH et al. *Proc ASH* 2013;Abstract 874 (abstract only).

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## Author Conclusions

- The infusion of autologous CD19-targeted CAR-modified T cells appears to be safe and has demonstrated promising antitumor efficacy to further improve CR rates in patients with high-risk CLL undergoing first-line purine analog-based chemotherapy.
- Although the number of treated patients in this study is too small to draw a definitive conclusion, the findings suggest that:
  - The second-generation CD19-targeted CAR-modified T cells elicit enhanced antitumor activity in patients with reduced disease burden.
  - Treatment with CD19-targeted CAR-modified T cells is more effective in eradicating disease in the bone marrow than in the lymph nodes.
- Enrollment to this study is ongoing.

Park JH et al. *Proc ASH* 2013;Abstract 874 (abstract only).

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### **Investigator Commentary: Ongoing Phase I Trial of Anti-CD19 CAR-Modified T Cells in CLL**

In this study, patients with previously untreated CLL with high-risk features other than persistent disease received standard induction PCR chemotherapy. Then, patients who achieved CR/PR with detectable MRD received genetically modified T cells. This is an interesting study that attempts to move the use of CAR-modified T cells to earlier settings as consolidation therapy for patients who one can predict will not fare well with conventional chemotherapy. It is known that patients who achieve a CR and have no MRD after conventional induction therapy have a long progression-free survival (PFS). However, patients with MRD after initial induction have a shorter PFS and overall survival. Therefore, the presence of MRD is a marker for subsequent poor outcome.

Only a small number of patients had received treatment at the time of the ASH presentation. It was a relatively limited study with a short follow-up. Of interest, the incidence of CRS was limited. This adds to other findings that seem to show that the degree of disease burden may predict the severity of CRS. All of the patients in this study had limited disease and did not experience severe CRS.

**(Continued)**

Two of the patients with persistent disease achieved a CR after T-cell infusion, 2 achieved a PR and 2 experienced PD. Although this study involved a small number of patients, it shows that one can potentially move this treatment strategy up front as consolidation after first-line therapy. This is the direction the field is and should be moving — trying to use this approach earlier in the course of the disease to prevent the disease from becoming refractory or extensive.

I believe that enough data will soon be generated to be able to move this strategy up as initial up-front treatment instead of consolidation therapy. It's early yet and we need more information about whether this approach will be effective for patients with low-burden disease. That would lend support to trying to use it as initial therapy in a chemotherapy-free regimen. An advantage over some of the newer therapies would be that this approach has the potential to be a "once-and-done" treatment if the CAR-modified T cells persist and are able to eradicate CLL. The patient may not need ongoing lifelong therapy as he or she would with some of the newer agents.

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

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