5 Minute JournalClub

POST-ASH Issue 7, 2014

CAR-Modified T Cells Directed Against CD19 in Relapsed/Refractory 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:

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Contracted Research: Novartis Pharmaceuticals Corporation; Other Remunerated Activities: Genentech BioOncology (faculty and spouse).

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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

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POST-ASH Issue 7, 2014

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

David L Porter, MD

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.

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-ζ 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**.

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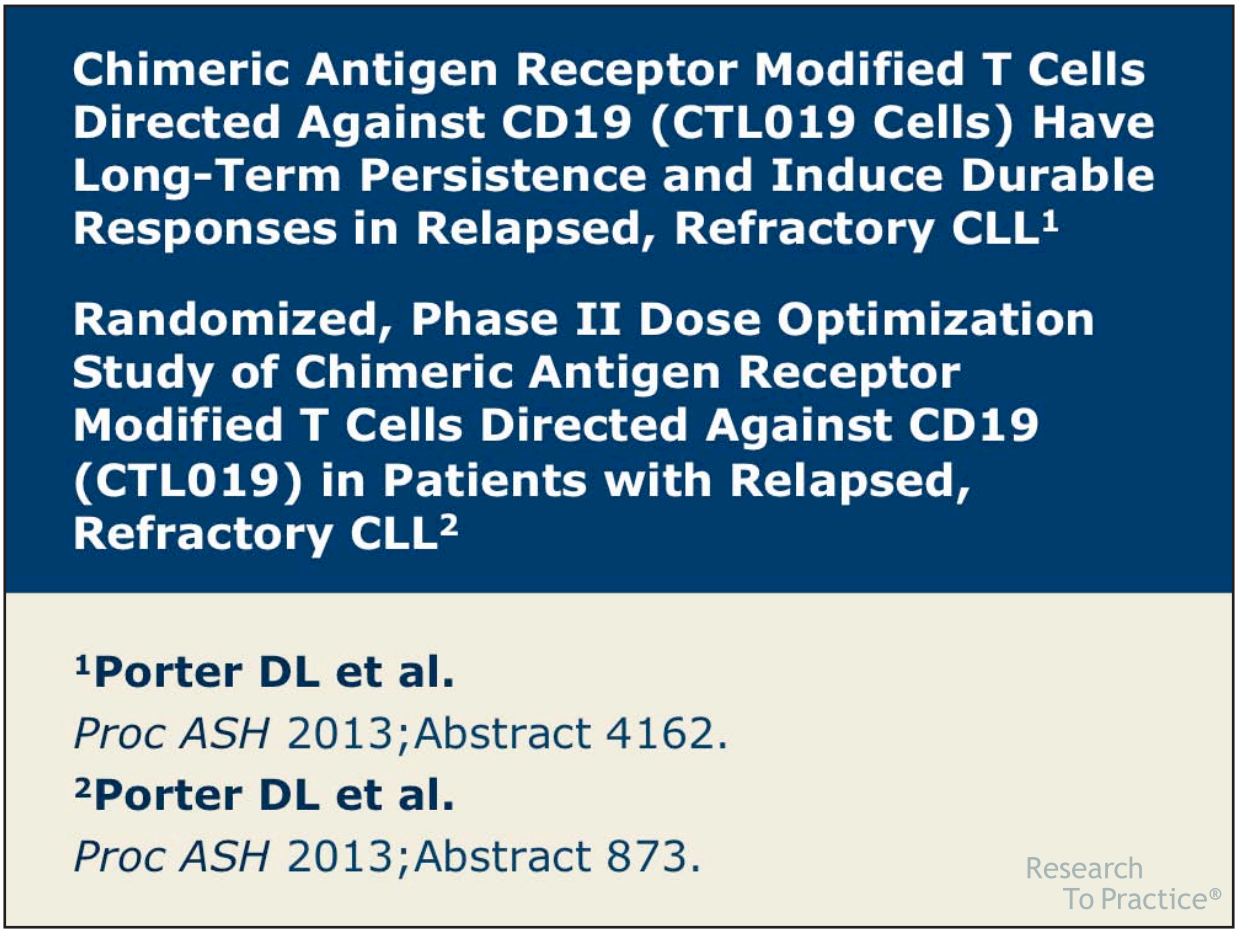
CAR-Modified T Cells Directed Against CD19 in Relapsed/ Refractory CLL

Presentations discussed in this issue

Porter DL et al. **Randomized, phase II dose optimization study of chimeric antigen receptor modified T cells directed against CD19 (CTL019) in patients with relapsed, refractory CLL.** *Proc ASH* 2013;**Abstract 873**.

Porter DL et al. **Chimeric antigen receptor modified T cells directed against CD19 (CTL019 cells) have long-term persistence and induce durable responses in relapsed, refractory CLL.** *Proc ASH* 2013;**Abstract 4162**.

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



Chimeric Antigen Receptor Modified T Cells Directed Against CD19 (CTL019 Cells) Have Long-Term Persistence and Induce Durable Responses in Relapsed, Refractory CLL

Porter DL et al.

Proc ASH 2013;Abstract 4162.

Background

- Patients with relapsed or refractory chronic lymphocytic leukemia (CLL) have poor prognoses.
- CD19, an antigen expressed on normal and malignant B cells, can be targeted with chimeric antigen receptors (CARs).
- CARs combine the antigen recognition domain of an antibody and intracellular signaling domains that mediate T-cell activation into a single chimeric protein.
- Inclusion of the CD137 (4-1BB) signaling domain results in potent antitumor activity and in vivo persistence of CAR-modified T cells in mice.
- Antitumor activity of CAR-modified autologous T cells targeted to CD19 (CTL019 cells) was observed in 3 patients with CLL with relatively short follow-up (*Sci Transl Med* 2011;3(95):95ra73).
- **Study objective:** To report on safety, feasibility and efficacy after longer follow-up of the pilot study with CTL019 cells in relapsed/ refractory CLL.

Porter DL et al. *Proc ASH* 2013;Abstract 4162.

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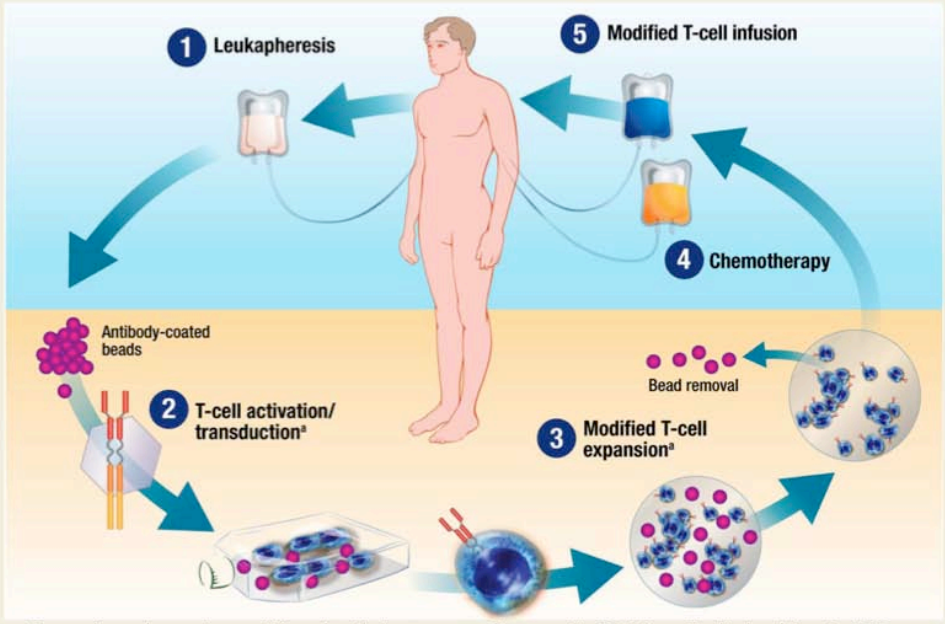
Study Methods

- Patients with relapsed/refractory, CD19+ CLL (n = 14)
  - Failed ≥2 therapies; progressed within 2 y of last therapy
- Autologous T cells were collected by leukapheresis
- The cells were transduced with a lentivirus encoding anti-CD19 single-chain variable fragment (scFv) linked to 4-1BB and CD3-ζ signaling domains
- Gene-modified T cells were expanded and activated ex vivo
- All patients received lymphocyte-depleting chemotherapy ending 3 to 5 days before cell infusion
- Target CTL019 cell dose 5 × 10^9 mononuclear cells
  - Transfection efficiency 10% to 40% (total dose 5 x 10^8 to 2 × 10^9)
  - Cell infusions over 3 days (10% d 1, 30% d 2, 60% d 3)

Porter DL et al. *Proc ASH* 2013;Abstract 4162.

Overview of CTL019 Therapy



[a] Transduced ex vivo with a lentivirus encoding anti-CD19 scFv linked to 4-1BB and CD3-ζ signaling domains

With permission from Porter DL et al. *Proc ASH* 2013;Abstract 4162.

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Response

Best response	n = 14
Overall response rate Complete response (CR)* Partial response (PR)	8 (57%) 4 (29%) 4 (29%)
No response	6 (43%)

* Minimal residual disease-negative

- All 4 patients who achieved CR had no evidence of disease (NED) in blood, bone marrow (BM) and lymph nodes (LN).
- Two patients who achieved PR experienced PR in blood, BM and LN.
- Two patients who achieved PR had NED in blood and BM but PR in LN.
- Cell expansion: Responders (n = 8): ≥2-3 logs
  Nonresponders (n = 6): none/minimal/<2 log

Porter DL et al. *Proc ASH* 2013;Abstract 4162.

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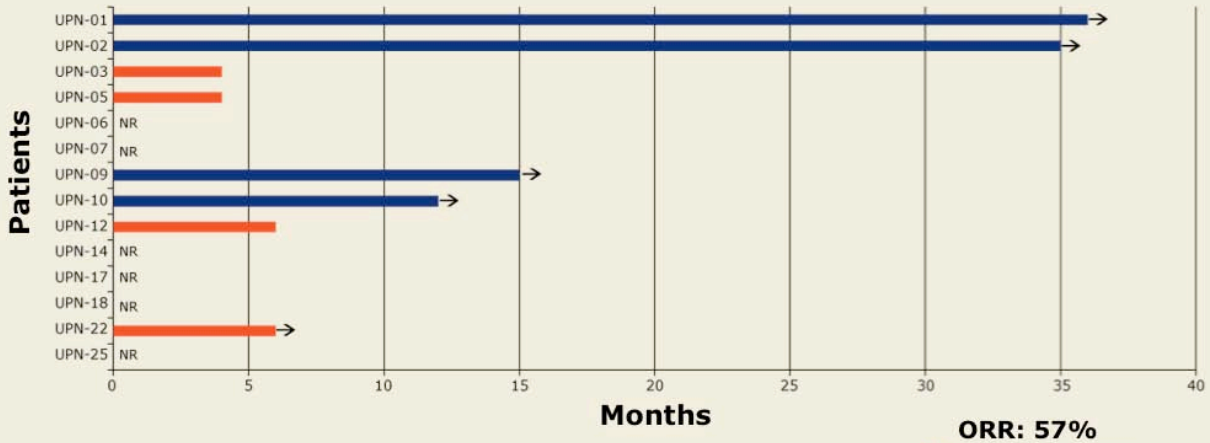
Duration of Response



- Median follow-up:
  - All patients: 12 mo (range 6-39)
  - Responding patients: 20 mo (range 6-39)

With permission from Porter DL et al. *Proc ASH* 2013;Abstract 4162.

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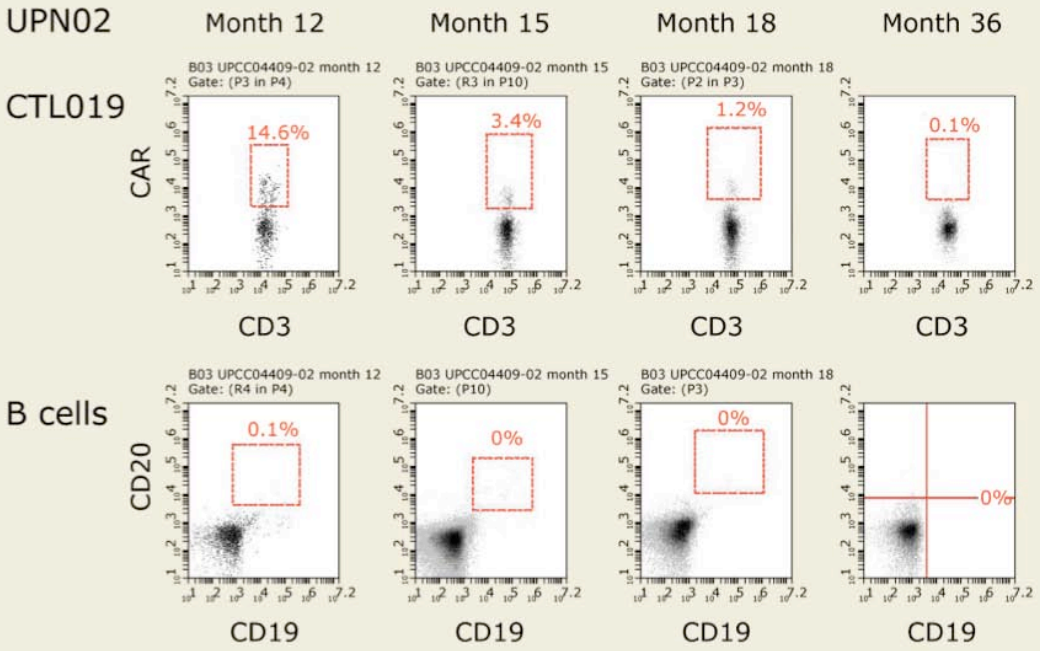
CTL019 Persistence and B-Cell Aplasia in a Patient with Relapsed/Refractory CLL



With permission from Porter DL et al. *Proc ASH* 2013;Abstract 4162.

Adverse Events

- Tumor lysis syndrome (TLS) (delayed, coincident with T-cell expansion)
- Hepatotoxicity (reversible, Grade 3/4 in 4 responding patients)
- Renal toxicity (Grade 3/4 in 4 patients)
  - Related to TLS, acute tubular necrosis from hypotension, reversible
- B-cell aplasia and hypogammaglobulinemia in all patients achieving CR, supported with intravenous immunoglobulin
  - No excessive or frequent infections
- Cytokine release syndrome (CRS) in all responding patients
  - High fever, myalgia, nausea, hypotension, hypoxia
  - High levels of interleukin-6 (IL-6), marked increase in interferon-gamma
  - Modest levels of TNF-alpha, mild increase in IL-2 levels
  - CRS rapidly reversed with steroids (n = 1) or tocilizumab (n = 4)
  - CRS associated with hemophagocytic lymphohistiocytosis/ macrophage-activating syndrome

Porter DL et al. *Proc ASH* 2013;Abstract 4162.

Author Conclusions

- Robust in vivo 1,000-fold to 10,000-fold expansion in CTL019 T cells
- Persistence for >36 months
  - Persisting cells are functional in vitro (data not shown)
  - Ongoing responses over many months and B-cell aplasia imply that persisting cells are functional in vivo
- Overall response rate in heavily pretreated CLL: 8/14 (57%) — 4 CR, 4 PR
- Eradication of bulky tumor
- Responses are durable: No patient in CR has relapsed; some patients with PRs cleared blood and BM with ongoing lymph node responses
- Responding patients developed B-cell aplasia and CRS
  - CRS treated effectively with anticytokine therapy
- No obvious dose-response or dose-toxicity effects as yet
- CAR therapy holds great promise for patients with hematologic cancers

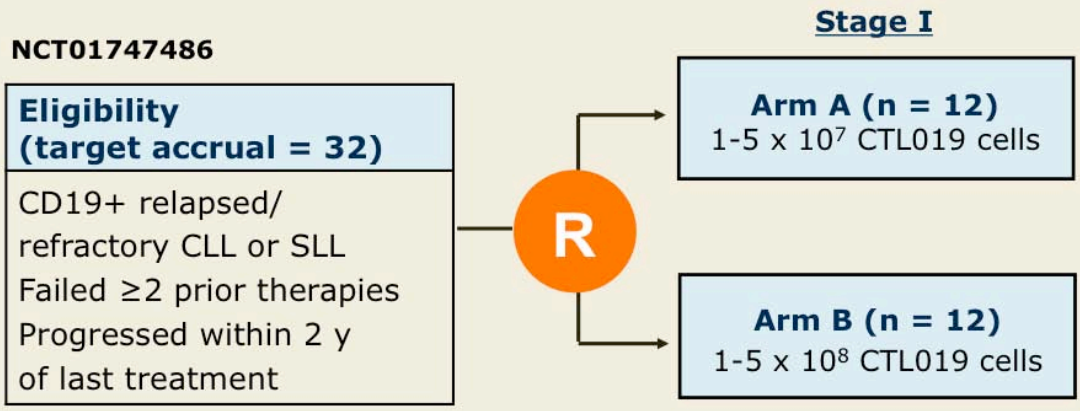
Porter DL et al. *Proc ASH* 2013;Abstract 4162.

Randomized, Phase II Dose Optimization Study of Chimeric Antigen Receptor Modified T Cells Directed Against CD19 (CTL019) in Patients with Relapsed, Refractory CLL

Porter DL et al.

Proc ASH 2013;Abstract 873.

Ongoing Phase II Study Design



SLL = small lymphocytic lymphoma

- **Primary endpoint:** CR at 3 months
- Stage II will enroll an additional 8 patients to the selected dose cohort when safety, tolerability and clinical responses have been evaluated to determine the optimal dose cohort.

Porter DL et al. *Proc ASH* 2013;Abstract 873.

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Response

Response rate	n = 18
Overall response rate	7 (39%)
CR	3 (17%)
PR	4 (22%)

- CRS in 6 of 7 responding patients
  - 5 of 11 patients with no response had CRS (p = 0.15 compared to responders)

Porter DL et al. *Proc ASH* 2013;Abstract 873.

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No Correlation between CTL019 Dose and Response or Toxicity

Response (n)	High dose (5×10^8)	Low dose (5×10^7)
Major response (CR + PR)	4	3
No response	5	6
Toxicity (n)	**High dose (5×10^8)**	**Low dose (5×10^7)**
CRS	5	6
No CRS	4	3

Porter DL et al. *Proc ASH* 2013;Abstract 873.

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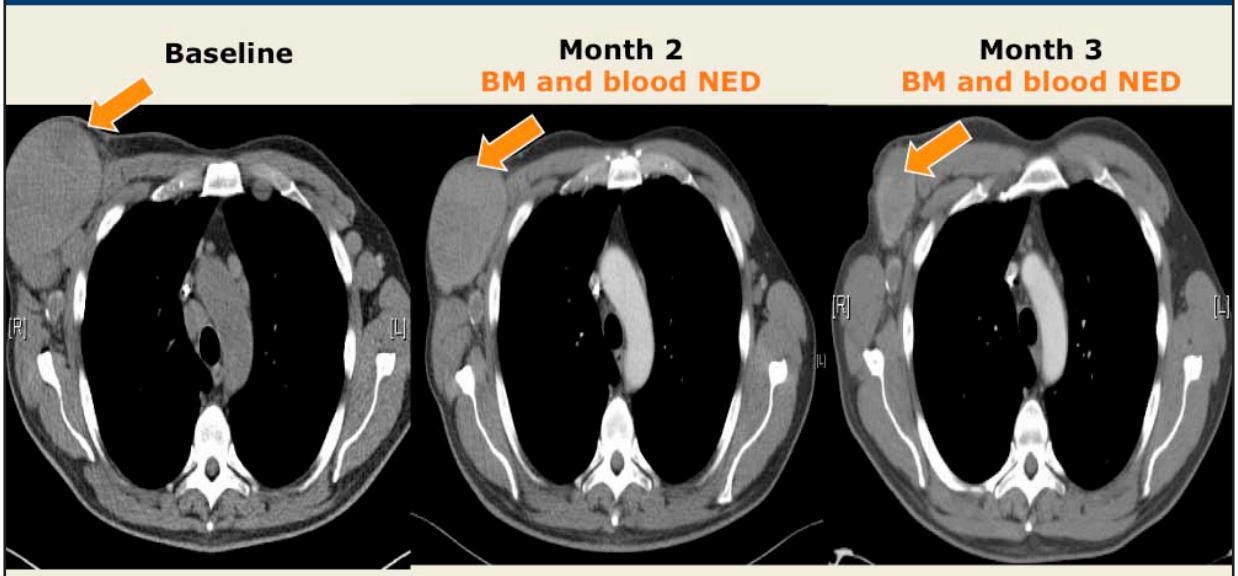
Ongoing Response in a Patient with Transformed CLL



10 prior therapies, transformed CLL, del(17p), ibrutinib resistant, XRT resistant

With permission from Porter DL et al. *Proc ASH* 2013;Abstract 873.

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Adverse Events

- No significant acute infusional toxicity
- Hepatotoxicity (1 reversible, Grade 3)
- TLS (3 Grade 3/4), reversible and manageable
- B-cell aplasia and hypogammaglobulinemia in responding patients, supported with intravenous immunoglobulin (IVIG)
  - No excessive or frequent infections
- CRS in 6 of 7 responding patients
  - High fever, myalgia, nausea, hypotension, hypoxia
  - High levels of IL-6, mild increase in IL-2
  - Modest levels of interferon-gamma and TNF-alpha
  - CRS rapidly reversed with tocilizumab
  - CRS associated with hemophagocytic lymphohistiocytosis/macrophage-activating syndrome

Porter DL et al. *Proc ASH* 2013;Abstract 873.

Author Conclusions

- Massive CTL019 expansion (1,000-fold to 10,000-fold in vivo)
- Overall response rate of 7 out of 18 (39%) in heavily pretreated CLL
  - 3 CR, 4 PR; several showing clearance of blood and bone marrow with ongoing lymph node responses
  - Eradication of bulky tumor
- Most responding patients develop CRS, which is treated effectively with supportive care and anti-IL-6 receptor antagonist therapy when needed
- No obvious dose-response or dose-toxicity effects as yet
- Responding patients develop B-cell aplasia
  - Hypogammaglobulinemia was treated with IVIG
- CAR therapy is promising for patients with advanced, relapsed/refractory CLL

Porter DL et al. *Proc ASH* 2013;Abstract 873.

Investigator Commentary: CAR-Modified T Cells Against CD19 in Relapsed/Refractory CLL

The first study, a pilot trial with 14 patients with relapsed/refractory CLL, aimed to assess the feasibility, safety and efficacy of CAR therapy. We reported an overall response rate of >50% with CAR therapy, even in patients with bulky disease and high-risk features.

One of the unique aspects of this study is that we were able to provide long-term follow-up, and 2 of the patients have been in remission for more than 3 years. In addition to long-term remission, we observed long-term persistence of the CAR T cells for more than 3 years. No correlation between dose and response or toxicity was seen. It was important to identify the optimal cell dose to establish consistency, and that led to the subsequent Phase II dose-optimization study.

That study randomly assigned patients to 2 doses of CTL019 cells. Both doses were used previously in patients who had responded. Again, no correlation between dose and toxicity or response was noted. The overall response rate was about 40%. Robust expansion of the CTL019 cells in the body occurred. This confirms our hypothesis that if T cells proliferate in vivo a lower dose can be administered. It may be useful to use a lower starting dose in certain situations if the activity is the same. The importance of this study will be to help define a therapeutic dose moving forward.

(Continued)

The CAR construct we use is unique in that it includes the 4-1BB costimulatory domain. This not only provides signals for T-cell activation through the costimulatory pathway but also provides survival signals to T cells. We believe that the 4-1BB domain may account for the long-term persistence of the modified T cells.

CRS was noted in responding patients and could be reversed with steroids and anti-IL-6 therapy. Responding patients also develop B-cell aplasia and hypogammaglobulinemia. We believe this to be an on-target effect because CD19 is present on normal B cells. To date, we have not observed any unexpected side effects from hypogammaglobulinemia, but these patients are being maintained with intravenous immunoglobulin repletion. B-cell aplasia is thought to be a marker of ongoing CAR T-cell activity.

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