5 Minute JournalClub

POST-ASH Issue 2, 2013

Chimeric Antigen Receptor T Cells Directed Against CD19 for Relapsed/Refractory CLL and ALL

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CME INFORMATION

OVERVIEW OF ACTIVITY

The annual American Society of Hematology (ASH) meeting is unmatched in its importance with regard to advancements in hematologic cancer and related disorders. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results and new information lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across virtually all malignant and benign hematologic disorders. As online access to posters and plenary presentations is not currently available, a need exists for additional resources to distill the information presented at the ASH annual meeting for those clinicians unable to attend but desiring to remain up to date on the new data released there. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists, hematologists and hematology-oncology fellows in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Appraise recent clinical research findings with lenalidomide/rituximab for patients with untreated indolent lymphoma and, where appropriate, counsel patients regarding participation in ongoing pivotal trials assessing this strategy.
- Evaluate the early efficacy and safety data with the anti-PD-1 monoclonal antibody pidilizumab (CT-011) for patients with relapsed/refractory FL.
- Assess the benefits and risks of novel therapeutic approaches — PI3 kinase inhibitors, Btk inhibitors and chimeric antigen receptor T cells — under investigation in B-cell neoplasms and, where appropriate, facilitate patient access to ongoing trials of these agents.
- Optimize outcomes for elderly patients with CLL through the application of emerging clinical research data.

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This activity is supported by educational grants from Celgene Corporation, Genentech BioOncology/Biogen Idec, Millennium: The Takeda Oncology Company, Seattle Genetics and Teva Oncology.

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: February 2013
Expiration date: February 2014

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POST-ASH Issue 2, 2013

ASH 2012 and the postrituximab era of new biologic treatments for B-cell neoplasms

To go directly to slides and commentary for this issue, **click here**.

Since the late 1990s rituximab (R) has been the major biologic agent integrated into management of B-cell cancers. However, these days some of the most cautious, evidence-based investigators are having a hard time hiding their enthusiasm for an array of emerging novel agents that are shaking up the non-Hodgkin lymphoma (NHL)/ chronic lymphocytic leukemia (CLL) research database. On this second issue of our 7-part ASH highlights series, we profile several promising new strategies, including a few that MD Anderson's Dr Hagop Kantarjian believes may soon lead to CML-like long-term disease control in CLL. Here's an overview of what we learned in Atlanta:

1. Small-molecule B-cell receptor inhibitors: Ibrutinib (Ib) and idelalisib (GS-1101)

These oral, relatively nontoxic agents interfere with the B-cell receptor signaling pathway and have intriguing activity in CLL, follicular lymphoma (FL) and mantle-cell lymphoma (MCL). Perhaps the greatest excitement surrounds Ib, an inhibitor of Bruton's tyrosine kinase, which is critical for proliferation and survival in most B-cell tumors. Ib was the subject of **2 spectacular CLL ASH papers**. The first was a Phase I-II monotherapy study of 116 patients that resulted in response rates Dr Bruce Cheson called "phenomenal" and exceeded 65% overall, including 12 of 24 patients with 17p and 11q deletions.

The second major related paper was a Phase II study evaluating the combination of Ib and R in 40 patients with previously treated high-risk CLL. I was struck by the title of the abstract, which states that this combination had "profound" activity. Given that description, the eye-popping **waterfall plots**, which pretty much all point south and included 13 patients with del 17p, were not that surprising. A highlight of this paper was the discussion of a patient who had primary resistance to FCR then hyper-CVAD and a number of other therapies but achieved a CR with Ib/R.

With regard to idelalisib, at ASH we saw findings from **a Phase I study** evaluating this PI3 kinase delta inhibitor combined with R and/or bendamustine (B) in 52 patients with relapsed/refractory (RR) CLL. PI3K delta is thought to drive proliferation and survival of malignant B cells, and as in many Phase I studies in this era of molecular-targeted treatment, most (about 80%) of the patients responded despite extensive prior treatments, including B and R. This well-tolerated combination approach is now being tested in Phase III trials.

2. Lenalidomide (len)

The first issue of this ASH series profiled immunomodulatory agents in multiple myeloma, including the newly approved pomalidomide, but this intriguing class of drugs clearly is also of great interest in B-cell cancers. The last several ASH meetings have included a number of presentations suggesting that len alone or with R ("R squared — R^2") has significant activity in CLL and NHL, and at the 2012 conference the good news continued.

Notably, Dr Nathan Fowler presented the final results of **a Phase II trial** of 110 patients with indolent lymphoma treated with the R^2 regimen. High rates of durable responses were observed, including CRs in 42/45 patients with FL who converted to PET negativity, and this encouraging data set and others have spawned a number of studies like the Phase III RELEVANCE trial comparing R^2 to chemotherapy/R, raising the possibility of a future world without chemotherapy for this disease.

Another Phase II CLL study evaluated a strategy now often used in myeloma, namely len maintenance, in this case for 12 months after BR induction. The encouraging median PFS of 24.3 months in 34 patients has led to interest in testing R^2 maintenance, an approach that is also the focus of a current ECOG MCL trial.

3. Other novel treatments: Chimeric antigen receptor (CAR) therapy, anti-PD-1

The spectacular science and clinical challenges of next-generation biologic therapy were on full display in a **paper profiling the use of CART19 cells** targeting the CD19 antigen, which is expressed on the surface of most B-cell cancers. This Star Wars-like treatment involves gene transfer techniques to genetically modify T cells, which in this study was demonstrated to have rapid and potent antitumor activity in chemotherapy-refractory CD19-positive CLL and ALL. The development of a cytokine release syndrome in some cases is a signal for caution in this maybe revolutionary approach to immune-based treatment.

Similarly, while anti-PD-1 has gotten a lot of press across solid tumor oncology, this immunotherapeutic strategy is also under investigation in hematologic cancers. In this regard, an **early paper** reported encouraging results with the combination of R and the anti-PD-1 monoclonal antibody pidilizumab (CT-011) in patients with RR FL.

While ASH was a treasure trove of exciting papers on biologics, more is on the way, as witnessed by a recent **press release** concerning a large Phase III German CLL trial evaluating the glycoengineered, humanized type II CD20 antibody obinutuzumab (O; GA101) that reported an advantage to adding this agent to chlorambucil (CLB), but this is just an appetizer to the main dish — the comparison to R-CLB. R seems to have less activity in CLL than in many lymphomas, and the hope is that O will yield greater benefit.

Next on this ASH series — new data on myelofibrosis, a cancer that finally has effective but complex treatment options, including 2 key follow-up reports of landmark Phase III trials of ruxolitinib.

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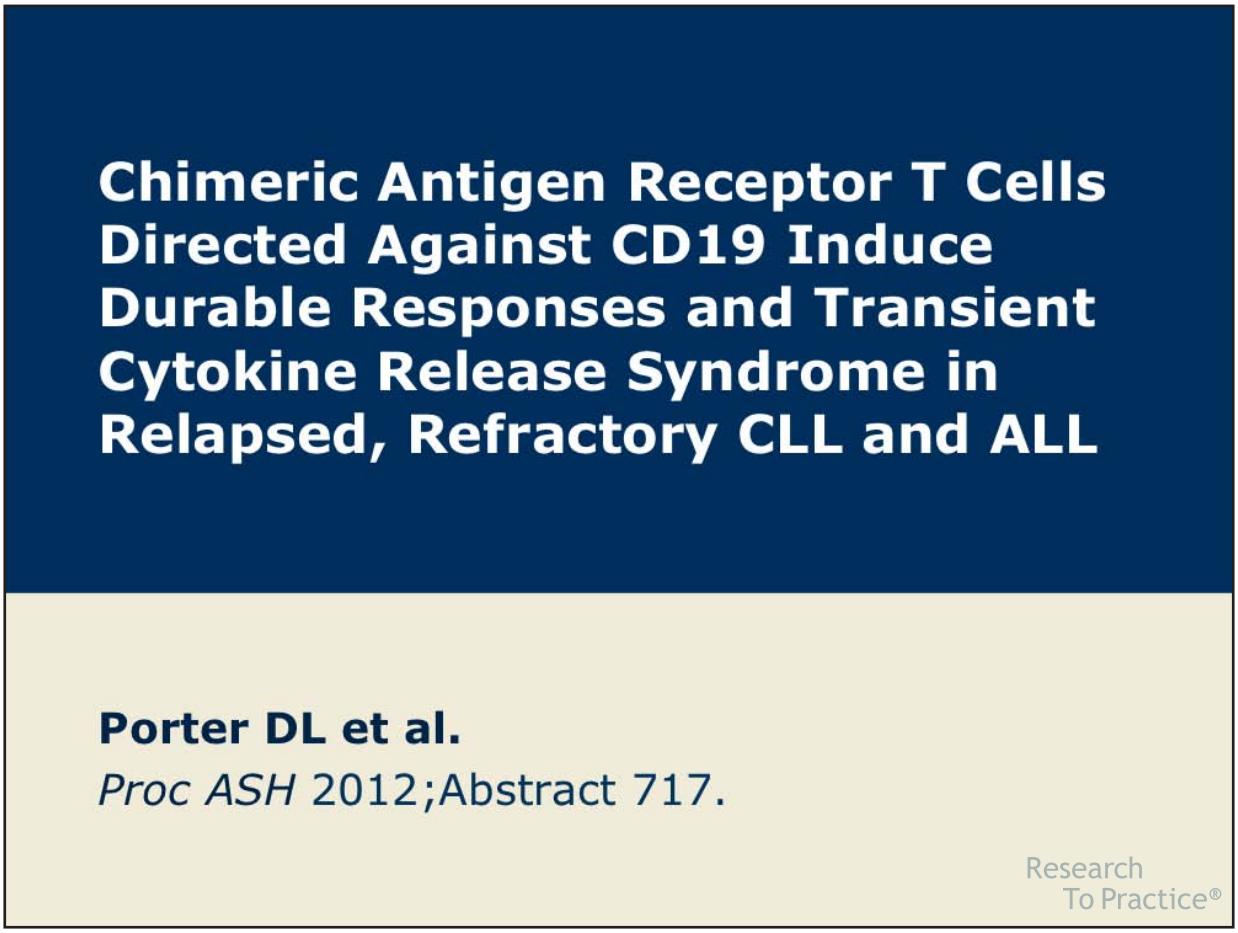
Chimeric Antigen Receptor T Cells Directed Against CD19 for Relapsed/Refractory CLL and ALL

Presentation discussed in this issue

Porter D et al. **Chimeric antigen receptor T cells directed against CD19 induce durable responses and transient cytokine release syndrome in relapsed, refractory CLL and ALL.** *Proc ASH* 2012;**Abstract 717**.

Slides from a presentation at ASH 2012 and transcribed comments from a recent interview with Brad S Kahl, MD (1/14/13)



Background

- Chimeric antigen receptors (CARs) combine the antigen recognition domain of an antibody with intracellular signaling domains into a single chimeric protein.
- CD19 is an ideal target for CARs because expression is restricted to normal and malignant B cells.
- With relatively short follow-up, initial data on antitumor activity of CAR-modified autologous T cells targeted to CD19 (CART19 cells) were reported for 3 patients with CLL (*NEJM* 2011;365:725; *Sci Transl Med* 2011;3:95ra73).
- **Study objective:** Present updated outcomes and longer follow-up analyses from 10 patients with relapsed/ refractory CLL or ALL treated with CART19 cells.

Porter DL et al. *Proc ASH* 2012;Abstract 717.

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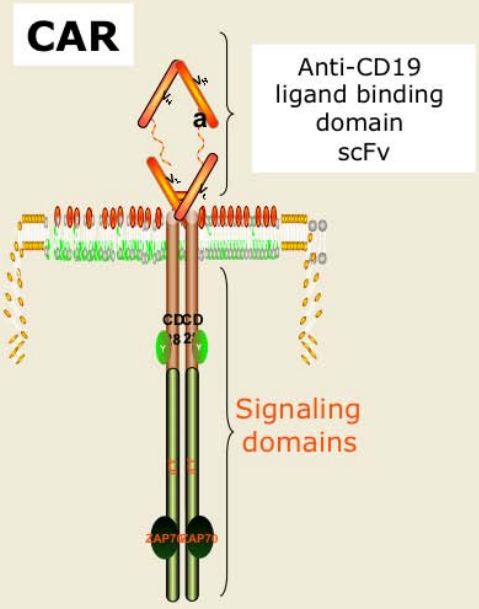
Treatment of Patients with CART19 Cells

- Autologous T cells collected by leukapheresis were transduced with a lentivirus encoding the anti-CD19 scFv linked to the 4-1BB (CD137) and CD3-z signaling domains.
- Gene-modified T cells were expanded and activated ex vivo by exposure to anti-CD3/CD28 beads.
- Ten patients received T-cell infusions containing a proportion of CART19 cells.
- Patients with CLL received lymphodepleting chemotherapy 4 to 7 days prior to infusion.
- Patients with ALL experienced chemorefractory relapse, received 6 weeks of chemotherapy prior to infusion and did not require further lymphodepletion.



With permission from Porter DL et al. *Proc ASH* 2012;Abstract 717.

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Study Design and Eligibility

- Single-center pilot trial of CTL019 (formally CART19) cells
- **Primary objective:**
  - Safety, feasibility and immunogenicity of CTL019 in patients with CD19-positive leukemia and lymphoma
- **Eligibility:**
  - CD19-positive B-cell malignancies with no available curative options (such as autologous or allogeneic stem cell transplant)
  - Failed ≥2 prior therapies, progression within 2 years of last treatment
  - Limited prognosis (<2 years) with available therapies

Porter DL et al. *Proc ASH* 2012;Abstract 717.

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Clinical Response

Pt UPN#	Blood	Marrow	Nodes	Expansion	Comments	Max resp
01	NED	NED	NED	>3 log	MRD* neg	CR 28 mo+
02	NED	NED	NED	>3 log	MRD* neg	CR 27 mo+
03	PR	PR	PR	2 log		PR 4 mo
04	PR	PR	PR	2 log		PR 4 mo
05	NR	NR	NR	<2 log		NR
06	NR	NR	NR	<2 log		NR
09	NED	NED	NED	>3 log	MRD* neg	CR 7 mo+
10	NED	NED	PR	2 log	Bulky nodes	PR 3 mo+
12	NED	NED	PR	2 log	Bulky nodes	PR 2 mo+
14	ne	ne	ne			ne

NED = no evidence of disease; MRD = minimal residual disease; CR = complete response; PR = partial response; ne = not evaluated

Porter DL et al. *Proc ASH* 2012;Abstract 717.

** MRD assessed with deep sequencing analysis*

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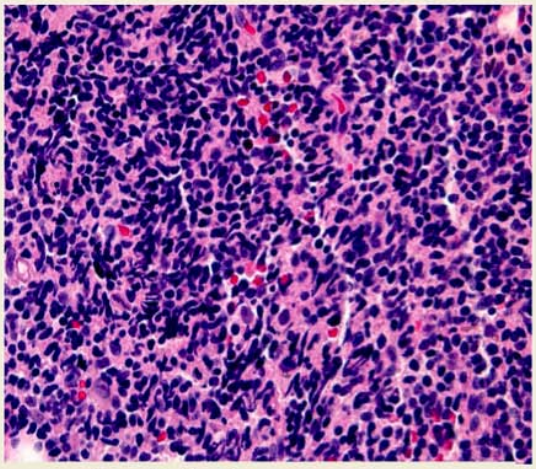
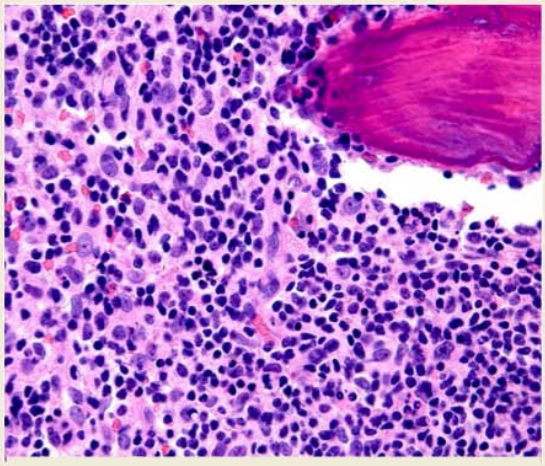
Marrow Response Observed in Patient UPN02



Pre-infusions marrow:
>50% involved by CLL (40x)



Day 31
No evidence CLL and negative by flow cytometry, cytogenetics, FISH or deep sequencing

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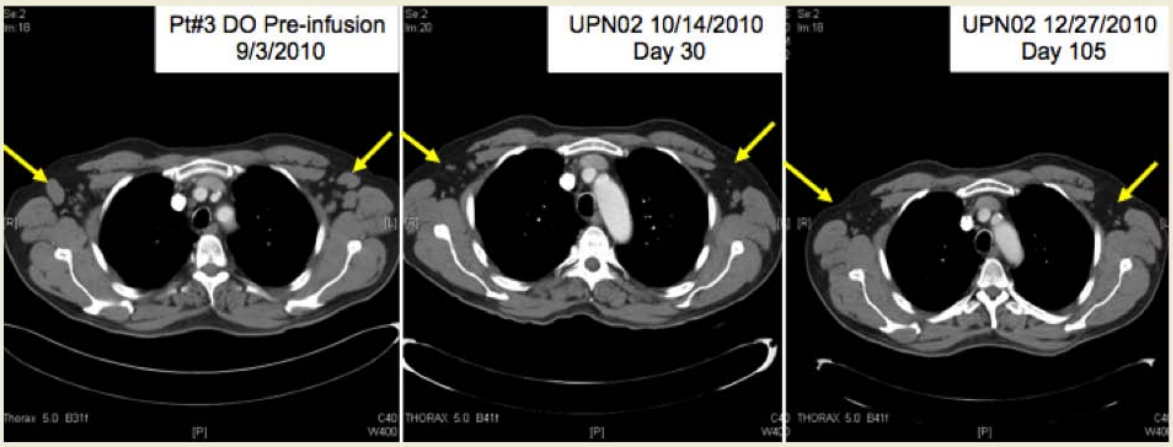
CT Response Observed in Patient UPN02



Response sustained >24 mo after CART-19 cell infusion

With permission from Porter DL et al. *Proc ASH* 2012;Abstract 717.

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Toxicity Summary of CTL019 (CART19)

- No significant infusional toxicity
- Hepatotoxicity (Grade 3-4 in 5 responding patients)
- Renal toxicity (Grade 3 in 1 patient)
  - Related to tumor lysis syndrome, acute tubular necrosis from hypotension
  - Reversible
- B-cell aplasia and hypogammaglobulinemia in patients achieving complete response
  - Treated with intravenous immunoglobulin
  - No excessive or frequent infections
- Tumor lysis syndrome
- Cytokine release syndrome

Porter DL et al. *Proc ASH* 2012;Abstract 717.

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CTL019 (CART19)-Associated Cytokine Release Syndrome (CRS)

- All responding patients developed a CRS at time of T-cell expansion
  - High fevers, nausea, hypotension, hypoxia, etc
- Associated with high levels of:
  - IL-6 (6-400x)
  - IFN-gamma (89-1,000)
  - IL-2R (5-25)
  - No significant increase in TNF-alpha, IL-2
- Immediately reversed with steroids (n = 1), steroids/ etanercept/tocilizumab (n = 1), tocilizumab (n = 2)

Porter DL et al. *Proc ASH* 2012;Abstract 717.

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Author Conclusions

- Autologous T cells genetically engineered to express an anti-CD19 scFv coupled to 4-1BB/CD3-z signaling domains can undergo robust in vivo expansion and persist for more than 2 years.
- CART19 cells can induce an overall response rate of 78%.
  - 3/9 complete and 4/9 partial responses, including CR in 2/2 patients with ALL
- Responding patients develop cytokine release syndrome, which can be treated effectively with anticytokine therapy.

Porter DL et al. *Proc ASH* 2012;Abstract 717.

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Investigator Commentary — CAR T Cells Directed Against CD19 Induce Durable Responses and Transient CRS in Relapsed, Refractory CLL and ALL

CAR-targeted therapy is designed for patients with cancer that expresses CD19. Most of the patients enrolled on this study have refractory CLL. Patients' T cells are harvested and genetically modified with a vector that will express a receptor that targets CD19. The cells are then infused back into the patient. It's a time-consuming and expensive procedure, but it definitely has merit. The authors have reported about 6 objective responses to date, some of which are CRs and are durable. This is a highly attractive strategy for ALL because once a patient experiences relapse we have no effective agents against this disease. I believe this strategy deserves more development in ALL. However, the challenge for this strategy in CLL is that we have some novel, easier-to-use and active agents — ibrutinib, ABT-199 — coming down the road. A few years ago this might have been the hottest strategy out there, but the field has changed so much that I'm a little skeptical that this therapy will make it to prime time in CLL.

Interview with Brad S Kahl, MD, January 17, 2013

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