642. CLL: THERAPY, EXCLUDING TRANSPLANTATION | NOVEMBER 15, 2013

Randomized, Phase II Dose Optimization Study Of Chimeric Antigen Receptor Modified T Cells Directed Against CD19 (CTL019) In Patients With Relapsed, Refractory CLL

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Abstract

Background

Patients (pts) with relapsed, and/or refractory (R/R) CLL have a poor prognosis with few effective treatment options. We have shown that infusion of autologous T cells genetically modified to express a chimeric antigen receptor (CAR) consisting of an external anti-CD19 domain, with the CD3ζ and 4-1BB signaling domains (CTL019 cells), can mediate potent anti-tumor effects in pts with advanced, relapsed refractory CLL. In our initial pilot study, doses of 1.7-50, x 10^8 mononuclear cells, corresponding to 0.14-5.9 x 10^8genetically modified cells, were given as a split dose infusion on days 0, 1 and 2 to 14 pts with R/R CLL and overall response rate (PR plus CR) was 57%. The majority of responses were sustained, and associated with marked expansion and long-term persistence of transduced cells. Notably, there was no obvious dose:reponse or dose:toxicity effect noted over a wide range of cell doses. To better define an optimal CTL019 cell dose, we are performing a randomized phase II study of 2 doses of CTL019 cells in pts with R/R CLL.

Methods

Pts with R/R CLL are randomly assigned to receive either 5x10^8 vs. 5x10^7transduced CTL019 cells, with the rationale that both doses induced CRs in pts on our initial pilot trial. In the initial stage, 12 evaluable pts will be treated in each arm and in stage 2, an additional 8 pts will be treated with the selected dose level. Pts have to have relapsed or persistent disease after at least 2 previous treatments and progress within 2 years of their last therapy. All pts receive lymphodepleting chemotherapy ending 3-5 days before T cell infusion. Cell infusions are given as a single dose.

Results

As of 7/15/2013, 27 pts have been enrolled; T cells did not adequately expand in 3, 1 patient was not eligible after screening, and 10 pts have been treated including 7 men and 3 women with a median age of 63 yrs (range 59-76). 5 pts had a mutation of p53. All pts had active disease at the time of CTL019 cell infusion. Lymphodepleting chemotherapy was Fludarabine/cyclophosphamide (8), pentostatin/cyclophosphamide (1), or bendamustine (1). 4 pts have been randomized to the higher dose level (5 x 10^8 CTL019 cells) and 6 pts have been randomized to the lower dose level (5 x 10^7CTL019 cells). There were no significant infusional toxicities. Median follow-up as of July 15, 2013 was 3 mo (1.3-5) for all pts and 3.3 mo (1.3-4) for responding pts. 2 pts have achieved a CR and 2 pts

overall response rate of 40%. In other recipients of CTL019 cells, we have observed ongoing improvement in adenopathy over time implying there can be a continued anti-tumor response. No responding patient has progressed. Seven of 10 pts experienced a delayed cytokine release syndrome (CRS) manifested by symptoms that included high fevers, nausea, myalgias and in some cases, capillary leak, hypoxia, and hypotension, typically correlated with peak CTL019 cell expansion.

We have noted that the CRS accompanying CTL019 therapy has been associated with marked increases of serum IL6 and can be rapidly reversed with the IL6-receptor antagonist tocilizumab. The CRS required intervention in 2 pts, one who responded and one who did not respond to CTL019. Treatment was initiated for hemodynamic or respiratory instability and was effective in reversing signs and symptoms of CRS in both pts.

A preliminary analysis through July 15, 2013 does not yet suggest a dose:response or dose:toxicity relationship. 2 of 4 recipients of the higher dose CTL019 responded, and 2 of 6 recipients at the lower dose level responded. The 7 pts who experienced a CRS included all 4 responding pts and 3 pts who did not respond. The CRS occurred in 3/4 recipients of higher dose CTL019 cells and 4/6 of recipients of lower dose CTL019 cells. CTL019 expansion in-vivo and persistence over the follow up period was noted in all responding pts.

Conclusions

In this ongoing dose optimization study of CTL019 cells, 4 of the first 10 pts treated have responded within 3 months. With short follow-up, as yet there is no suggestion that there is a dose:response or dose:toxicity relationship at the dose ranges being studied. These cells can undergo robust in-vivo expansion and from other studies (ASH 2013) can persist for at least 3 yrs. This trial confirms that CTL019 cells can induce potent responses for pts with advanced, relapsed and refractory CLL.

Disclosures:

Porter:*Novatis:* IP and potential royalties with COI managed according to policies of the University of Pennsylvania, IP and potential royalties with COI managed according to policies of the University of Pennsylvania Patents & Royalties, Research Funding; *Genentech:* Spouse employment, Spouse employment Other. **Off Label Use:** CTL019 cells to treat CLL. **Kalos:***Novartis corporation:* CART19 technology, CART19 technology Patents & Royalties; *Adaptive biotechnologies:* Member scientific advisory board , Member scientific advisory board Other. **Grupp:***Novartis:* Research Funding. **Chew:***Novartis:* Patents & Royalties. **Shen:***Novartis Pharmaceuticals:* Employment, Equity Ownership. **Wood:***Novartis Pharmaceuticals:* Employment, Equity Ownership. **Litchman:***Novartis Pharmaceuticals Corporation:* Employment, Equity Ownership. **Zheng:***Novartis:* Patents & Royalties. **Levine:***Novartis:* cell and gene therapy IP, cell and gene therapy IP Patents & Royalties. **June:***Novartis:* Patents & Royalties, Research Funding.

Topics: cd19 antigens, chimeric antigen receptors, chronic lymphocytic leukemia refractory, t-lymphocytes, brachial plexus neuritis, infusion procedures, toxic effect, follow-up, chemotherapy regimen, cyclophosphamide

Author notes

* Asterisk with author names denotes non-ASH members.