MINI REVIEW

Tumor Antigen Escape from CAR T-cell Therapy

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ABSTRACT

Emerging data from chimeric antigen receptor (CAR) T-cell trials in B-cell malignancies demonstrate that a common mechanism of resistance to this novel class of therapeutics is the emergence of tumors with loss or downregulation of the target antigen. Antigen loss or antigen-low escape is likely to emerge as an even greater barrier to success in solid tumors, which manifest greater heterogeneity in target antigen expression. Potential approaches to overcome this challenge include engineering CAR T cells to achieve multispecificity and to respond to lower levels of target antigen and more efficient induction of natural antitumor immune responses as a result of CAR-induced inflammation. In this article, we review the evidence to date for antigen escape and downregulation and discuss approaches currently under study to overcome these obstacles.

Significance: Antigen escape and downregulation have emerged as major issues impacting the durability of CAR T-cell therapy. Here, we explore their incidence and ways to overcome these obstacles in order to improve clinical outcomes.

INTRODUCTION

Adoptive T-cell therapy for cancer was pioneered by Rosenberg and colleagues at the NCI. Tumor-infiltrating lymphocytes (TIL) were surgically harvested, expanded ex vivo, and infused back into the patient, inducing complete responses (CR) in approximately 20% of patients with metastatic melanoma, and firmly establishing the clinical potential for T cells to exert antitumor activity in humans (1–3). TILs express natural T-cell receptors (TCR) that can recognize antigens expressed by a patient’s tumor in an MHC-restricted manner. In an attempt to develop receptors capable of tumor antigen recognition independent of MHC expression, researchers developed chimeric antigen receptors (CAR). Groups led by Eshhar and Kuwana first fused the heavy and light chain variable regions of a monoclonal antibody to the constant regions of the TCR and demonstrated that these synthetic receptors can recognize antigen and enact T-cell effector functions (4, 5). Drawing on the finding that CD3ζ is the master switch for T-cell activation (6), CARs were simplified to contain only the CD3ζ component of the TCR. The addition of CD28 and other costimulatory domains increased the potency and persistence of CARs (7), resulting in highly effective therapeutics that have demonstrated remarkable clinical activity (8–15).

CAR T cells are transforming the care of patients with relapsed and refractory B-cell malignancies. Early-phase clinical trials demonstrate robust efficacy that has led to FDA approval of two CD19 CAR T-cell products, tisagenlecleucel and axicabtagene ciloleucel (16, 17). However, careful follow-up of patients treated with CAR-based therapies for B-cell malignancies has demonstrated a high rate of post-therapy relapse through acquired tumor resistance (18). Most commonly, immune pressure by CAR T cells drives cancers to evolve by modulating expression of their target antigens, through either loss of detectable antigen or diminished expression of the antigen to a level below a threshold required for CAR T-cell activity. In this article, we review the evidence for tumor resistance to CAR therapeutics via the emergence of antigen-negative/low variants and discuss approaches that could be undertaken to overcome this problem.

ANTIGEN LOSS: CLINICAL DATA

Initial reports from phase I trials of CD19 CAR T cells in pediatric B-cell acute lymphoblastic leukemia (B-ALL) demonstrated response rates ranging from 70% to 90% (8–10), and similarly impressive results were seen in adults (11, 14, 15). However, the durability of these responses was sometimes limited by the outgrowth of CD19-negative leukemia, especially in patients whose CAR T cells persist for long periods. In the first publication of a phase I trial of a CD19-4-1BBζ CAR for pediatric B-ALL from the Children’s Hospital of Philadelphia (CHOP), 3 of 27 (11%) responders relapsed with leukemia without detectable CD19 (8). An abstract from CHOP with longer...
follow-up from these initial patients, which also included additional treated patients, reported that 13 of 55 patients (24%) who had a CR experienced a CD19-negative relapse (19). In a global phase II trial of Novartis’s tisagenlecleucel, among 16 relapses characterized for CD19 expression, 15 were demonstrated to be CD19-negative. Therefore, with limited follow-up, at least 15 of 61 (25%) complete responders went on to develop CD19-negative or partially negative relapse (an additional six relapses were not analyzed for CD19 expression; ref. 17). In a clinical trial from Seattle Children’s Research Institute (SCRI) of a similar CD19-4-1BB-ζ CAR for B-ALL, 7 of 40 patients (18%) who achieved a CR later relapsed with loss of CD19 (10).

A trial of a CD19-CD28-ζ CAR at the NCI in pediatric patients was marked by shorter T-cell persistence and patients frequently underwent hematopoietic stem cell transplant (HSCT) after CAR therapy, but 2 of 12 patients who had achieved a minimal residual disease (MRD)–negative response also developed CD19-negative B-ALL (neither patient underwent HSCT; ref. 9). A follow-up report in abstract form that included expansion cohorts from the NCI study indicated that 5 of 28 patients (18%) who were MRD-negative after CAR eventually relapsed with diminished expression of CD19, including some patients who relapsed following HSCT (20). Data from post-CAR relapses of adults with B-ALL are scant: The Fred Hutchinson Cancer Center (FHCC) phase I trial of a CD19-4-1BB-ζ CAR found CD19-negative relapses in 2 of 29 patients (7%) who achieved a CR (11). Similarly, a trial from Memorial Sloan Kettering Cancer Center (MSKCC) of a CD19-CD28-ζ CAR in adults with B-ALL saw CD19-negative leukemia in only 4 of 44 patients (9%) achieving a CR (21). The reason for the lower rates of CD19-negative leukemia in trials of adults versus children is unclear. The shorter persistence of the CD19-CD28-ζ CAR T cells employed by MSKCC may partially explain the low rate of CD19-negative relapse in their trial, as a shortened period of immune pressure due to the limited persistence of the CD19-CD28-ζ CAR could diminish the risk of antigen loss escape (21). Similarly, most post-CR relapses in the FHCC trial were CD19-positive relapses among patients who did not receive fludarabine as part of their conditioning regimen, which has been shown to limit the persistence of CAR T cells (11). A summary of the rate of CD19-negative relapse in CD19 CAR trials for B-ALL can be found in Table 1, although caution should be taken when comparing across studies given that they differ greatly in the period of follow-up. CD19-negative relapse of B-ALL is also observed after treatment with the bispecific T-cell engager blinatumomab (CD3 × CD19), occurring in 12% to 21% of complete responders, depending on the study (22–24). In summary, although CD19-negative escape is a major cause of relapse following CD19-CAR therapy for B-ALL, the true incidence of this phenomenon has not been defined and factors that predict for an increased likelihood of CD19-negative relapse are poorly understood. Nonetheless, as the application of CD19-directed immunotherapy with both CD19 CARs and blinatumomab grows, it is clear that the clinical impact of CD19-negative B-ALL will increase as well.

Table 1. A summary of antigen escape in CD19 CAR trials for ALL

<table>
<thead>
<tr>
<th>Trial Population CD19 CAR construct</th>
<th>Relapse rate (n/N)</th>
<th>CD19-negative relapse rate (n/N)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children’s Hospital of Philadelphia phase I Pediatric FMC63-4-1BB-ζ</td>
<td>36% (20/55)</td>
<td>24% (13/55)</td>
<td>8, 19</td>
</tr>
<tr>
<td>Novartis phase II (ELIANA) Pediatric FMC63-4-1BB-ζ</td>
<td>33% (20/61)</td>
<td>25% (15/61)</td>
<td>17</td>
</tr>
<tr>
<td>Seattle Children's Research Institute phase I Pediatric FMC63-4-1BB-ζ</td>
<td>45% (18/40)</td>
<td>18% (7/40)</td>
<td>33</td>
</tr>
<tr>
<td>NCI phase I Pediatric FMC63-CD28-ζ</td>
<td>29% (8/28)</td>
<td>18% (5/28)</td>
<td>9, 20</td>
</tr>
<tr>
<td>Memorial Sloan Kettering phase I Adult SJ25C1-CD28-ζ</td>
<td>57% (25/44)</td>
<td>9% (4/44)</td>
<td>21</td>
</tr>
<tr>
<td>Fred Hutchinson Cancer Center phase I Adult FMC63-4-1BB-ζ</td>
<td>31% (9/29)</td>
<td>7% (2/29)</td>
<td>11</td>
</tr>
</tbody>
</table>

In a combined analysis of phase I and phase II trials of axicabtagene ciloleucel for NHL, of the 11 patients who progressed after having a response to CD19 CAR and also had tissue available for analysis, 3 patients had biopsy proven CD19 loss by IHC (16). Notably, however, a very stringent cutoff (<1% of cells expressing CD19) was used for negativity in this assessment, and it remains possible that a higher frequency of patients could have experienced emergence of CD19 antigen loss that contributed to relapse. In a trial at the University of Pennsylvania of a CD19 CAR for NHL, 5 nonresponders underwent postinfusion biopsies and one demonstrated absent CD19 expression (25). Other cases of CD19-negative lymphoma following CD19-CAR therapy have been reported by CHOP and the NCI in pediatric patients (26, 27) and by the NCI in an adult (28). Together, the data demonstrate that emergence of antigen loss variants is the most common cause of relapse following CD19-CAR therapy for B-ALL, and emerging data provide evidence that CD19-negative relapses also occur in NHL, although the
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incidence of this phenomenon remains less clear. Furthermore, loss of target antigen has also been observed in a patient with multiple myeloma treated with a CAR targeting BCMA (29) as well as in patients with glioblastoma multiforme who were treated with CARs targeting either EGFRvIII (30) or IL13Rα2 (31).

ANTIGEN LOSS: MECHANISM

Given the large clinical experience of CD19 CARs in pediatric B-ALL, most data regarding the mechanism of antigen loss come from studies of patient samples in those trials (10, 32, 33). Thus far, the published data have demonstrated CD19 loss occurring via two distinct mechanisms: antigen escape or lineage switch (34). In antigen escape, after achieving a remission in response to CD19 CAR, patients relapse with a phenotypically similar disease that lacks surface expression of a CD19 molecule capable of binding the anti-CD19 antibodies incorporated into the CARs. Lineage switch occurs when a patient relapses with a genetically related but phenotypically different malignancy, most often acute myeloid leukemia (AML; Fig. 1).

The group at the CHOP described mechanisms responsible for at least some of the antigen escape seen in pediatric patients with B-ALL after CD19 CAR. Sotillo and colleagues found several CD19 splice variants expressed by B-ALL, including Δexon-2, which specifically lacks the exon containing the extracellular epitope of CD19 recognized by both the FMC63 (CHOP-University of Pennsylvania/Novartis, NCI/Kite, FHCC-SCRI/Juno-JCAR017) and SJ25C1 (MSKCC/Juno-JCAR015) anti-CD19 binders. In addition, they observed variants Δexon-5,6, which lack the transmembrane domain of CD19 and therefore lead to loss of surface expression. Immune pressure by the CD19 CAR results in selection of leukemia cells expressing higher proportions of these splice variants, leading to escape from detection by CD19 CAR T cells (32). Recent work suggests that patients with ALL already express CD19 splice variants at diagnosis and therefore anti-CD19 therapy may simply select for cells that express these alternative forms of CD19 (35). This mechanism does not account for all cases of CD19 loss in cells that retain a B-ALL phenotype, and other mechanisms merit exploration (36). For instance, one group reported a single patient with loss of CD81, a chaperone protein for CD19, as a mechanism for CD19 loss after blinatumomab (37).

Lineage switch is another mechanism for CD19 loss that has been observed in clinical trials (33). Most often seen in patients who harbor MLL rearrangements, such as infants with B-ALL, lineage switch occurs when the leukemic phenotype changes from lymphoid to myeloid in response to CD19-directed immunotherapy. The evolved leukemic population not only no longer expresses CD19, but also acquires other phenotypic characteristics of AML. This was observed in 2 pediatric patients with MLL-rearranged ALL treated with CD19 CAR on the SCRI trial (33) and one adult on the CD19 CAR trial at the FHCC (11). In addition, this phenomenon was modeled in a murine leukemia by Jacoby and colleagues, who demonstrated that CD19 CAR induces lineage switch in a murine ALL model that is dependent on the E2a:PBX transgene, which, like MLL rearrangement, can drive the development of either lymphoid or myeloid neoplasms (36). Lineage switch has also occurred in both MLL-rearranged and nonrearranged patients after CD19-directed therapy with blinatumomab (38–40). Similarly, a single case of CLL that transformed to a clonally related plasmablastic lymphoma after CD19 CAR treatment has been reported (41).

OVERCOMING ANTIGEN LOSS

Delineation of the multitude of mechanisms involved in CD19 antigen loss suggests that creating CARs to target alternative epitopes on CD19 may not prove effective, because many of the examples involve loss of CD19 surface expression. The data also suggest that neither CD19-CAR nor...
blinatumomab-mediated T-cell killing drives meaningful induction of immune responses to coexisting immunogenic targets on B-ALL, sometimes referred to as “epitope spreading.” This may reflect the relative low tumor mutational burden in B-ALL, which likely limits inherent immunogenicity of this disease (34, 42). In addition, the use of lymphodepleting agents prior to adoptive transfer of T cells could blunt the native immune response as host T cells are depleted, similar to what has been observed in murine models. In one study, Pmel-1 T cells recognizing gp100 were adoptively transferred to lymphopenic versus lymphoreplete mice bearing B16 melanomas. This therapy was found to be more effective in lymphoreplete animals, largely due to enhanced epitope spreading (43).

Thus far, the degree to which epitope spreading is induced by CAR T cells has been incompletely studied. In a murine CAR model targeting EGFR, mice that were cured of EGFR+ tumors by EGFR CAR T cells later rejected EGFR+ tumors when rechallenged (44). This elegant model demonstrated that epitope spreading can be induced by CAR T cells, but it is unclear to what extent this occurs in human studies and whether the incidence of this phenomenon might be more common if effective CAR-based therapeutics were used to target tumors with higher inherent immunogenicity. One clinical trial of a CAR targeting mesothelin did find that patients who received CAR T cells also developed an antitumor antibody response (45). It is possible that combining CAR T cells with radiation (46), checkpoint inhibition (47–49), vaccines (50, 51), or other immune agonists (34, 52) will result in epitope spreading that could help counter immune escape, and we anticipate such studies will emerge as the field matures.

Another approach to overcoming antigen loss following CAR T-cell therapy is to simultaneously target more than one antigen on cancer cells, an approach that is compelling for B-ALL, given that CD22 CAR T cells have also demonstrated substantial clinical efficacy (53). There are several ways to engineer a T-cell product for multispecificity (Fig. 2). T-cell products that are separately transduced for different CARs can be simultaneously or sequentially administered (“coadministration”; Fig. 2; ref. 54), or vectors for two CARs can be combined during cell production to achieve a mixed product with some cells that are positive for a single CAR and others that are positive for both CARs (“cotransduction”; Fig. 2). The disadvantages of these approaches are the high cost of producing multiple vectors and the heterogeneity of the infused product, which can complicate clinical analysis.

A CAR molecule itself can also be engineered to recognize multiple antigens. This can be accomplished by linking two binders on a single molecule (“tandem CAR”; Fig. 2), which appears, in some cases, to enhance the strength of the immune synapse. Hegde and colleagues developed a tandem CAR that can simultaneously target both HER2 and IL13Rα2. They demonstrated enhanced potency and antitumor activity in vivo when two CARs were expressed as a single molecule compared with expressing two separate CARs individually on each T cell or coinfusing two populations of cells, each expressing a monospecific receptor (55). In designing so-called tandem CARs, the position of the target antigen should determine how each binder is oriented relative to the membrane. For instance, in a study of a tandem CD19-CD20 bispecific CAR, the authors found that given the proximal location of CD20 to the cell membrane, the anti-CD20 ScFv needed to be in the distal position in the CAR molecule (56).

Alternatively, two or three separate CARs can be expressed on a single T cell using a single vector by taking advantage of ribosomal skip sequences or internal ribosomal entry sites (“bicistronic CAR”; Fig. 2). Recently, a trivalent vector encoding three independent CARs, each targeting a different antigen on glioblastoma, was described (57). It is likely that over the next several years, multiple methods for creating...
multispecific CARs will be evaluated and compared for efficacy in both preclinical and clinical settings.

Several clinical trials are under way testing multispecific CAR T cells. We recently reported on a tandem CAR targeting both CD19 and CD22 (53) that is now in clinical trials in children and adults (NCT03241940, NCT03238354, and NCT03448393), and other groups have generated tandem CARs targeting CD19 and CD20 (56, 58, 59), one of which is currently being tested in humans (NCT03019055). The mixed product approach is currently being explored in a clinical trial for pediatric B-ALL targeting CD19 and CD22 (NCT03330691). An abstract was recently presented for a trispecific CAR recognizing CD19, CD20, and CD22 (60). In addition, one group has reported a bispecific CD19 and CD123 CAR in the aims of overcoming both antigen escape and lineage switch as CD123 is expressed broadly in the hematopoietic compartment (61), although such an agent would be expected to induce substantial hematopoietic toxicity (62). We anticipate increasing numbers of trials testing CARs capable of simultaneously targeting two or more antigens in the near term.

**LOW ANTIGEN DENSITY: CLINICAL DATA**

In recognizing that single antigen targeting was unlikely to be successful in many cases of pediatric B-ALL, we developed a CAR targeting CD22, another B-cell antigen broadly expressed on lymphoblasts (63). In the first clinical trial of this CAR in B-ALL, we observed a high remission rate in patients with both CD19-negative and CD19-positive disease. However, 8 of 12 patients (67%) attaining a CR relapsed within 12 months after CD22-CAR infusion and at the time of relapse, CD22 expression was retained in 7 patients, albeit at lower levels than observed at the time of CD22-CAR therapy. The diminished expression of CD22 was not accompanied by any detected mutations at the genomic level or diminished expression of CD22 mRNA, suggesting that downregulation of CD22 expression occurs at a posttranscriptional level. In several patients, both CD22-low lymphoblasts and persistent anti-CD22-CAR T cells were found in the bone marrow, indicating that the CAR was unable to effectively eliminate CD22-low cells (53). This was further demonstrated by generating leukemia lines with variable CD22 expression levels, and directly demonstrating that the capacity for the CD22 CAR to produce cytokine and control tumor cells in xenograft models was exquisitely dependent upon surface expression levels of CD22.

However, this mechanism of escape is consistent with substantial emerging data regarding CAR T-cell activation requirements. We and others have demonstrated the need for high target antigen density in order for CARs to fully activate and exert in vivo activity (64–66). This was recently described in detail in studies focused on a CAR targeting anaplastic lymphoma kinase (ALK), wherein cytokine production was highly dependent upon antigen expression levels, with submaximal levels observed below 10,000 molecules/cell. As a result, although cell lines engineered to express very high levels of ALK were readily eradicated in vivo, those expressing physiologic levels were not controlled by ALK-CAR T cells. Whether the activity of CD19-CAR T cells might be limited by insufficient CD19 expression remains unknown. This seems unlikely in B-ALL, because the pattern of CD19 expression in this disease appears to be homogeneously high. However, CD19 expression in CAR trials for NHL has not been systematically studied, as researchers have largely relied on IHC where quantification is unreliable (16).

The biological basis for the requirement for high target antigen levels for optimal CAR T-cell activity remains incompletely understood, but could reflect limitations in the nature of antigen recognition by CAR receptors (Fig. 1). Natural TCRs are capable of recognizing antigen at low density, making it tempting to speculate that the differences in antigen density requirements may emerge from the dramatic differences in structure between natural TCRs and CARs. CARs are elegant in their simplicity, but are also a crude imitation of the highly evolved system of TCR antigen recognition. Natural TCRs contain several signaling domains (gamma, delta, epsilon, zeta), whereas CARs typically incorporate TCRζ as the sole TCR signaling element. Although data suggest that signals downstream of TCRζ largely replicate that of the complete TCR signaling complex (6, 67), this matter remains incompletely investigated. Furthermore, during the course of antigen recognition, natural TCRs create a highly organized immune synapse that incorporates coreceptors to enable recognition of very low antigen density (68, 69). Emerging studies demonstrate that the immune synapse created when CARs recognize antigen is less organized than that of a natural TCR (70). Finally, the nature of antigen binding itself differs substantially between the TCR and the CAR receptor, because TCRs are low-affinity binders (Kd in the micromolar range), whereas scFvs incorporated into most CARs recognize antigen with very high affinity (Kd in nanomolar range; ref. 71). These distinctions are likely to significantly affect the quality of responses induced in T cells expressing CARs as compared with natural TCRs (72), but the full extent of the distinctions remains incompletely characterized.

The recognition that CARs require high antigen expression for significant activity has numerous implications for the future development of these therapeutics for solid tumors. Given that nearly all targets on solid tumors for which clinical trials of CAR T cells are planned are heterogeneous and not all tumors for which clinical trials of CARs targeting solid tumors become more potent, clinical successes will be limited by the rapid selection of antigen low variants. CARs for AML face similar hurdles (77). Alternatively, a CAR T-cell requirement for high antigen density also opens the possibility of a therapeutic window based upon differential target antigen density between malignant and nonmalignant tissues. The potential for CAR T cells to attack normal tissues based upon low levels of antigen has been debated at length as a result of a fatal event in a single patient treated with a CAR targeting HER2 at the NCI. This patient died of cardiovascular collapse following infusion of 10e10 Her2-28-41BB-ζ CAR T cells (78, 79). CAR T-cell infiltration was found in the patient’s lungs and the cause of death was initially attributed to on-target, off-tumor toxicity. However, additional insights regarding the pathophysiology of cytokine release syndrome (CRS) following CAR T-cell therapeutics suggest that cardiovascular collapse in this patient was more likely related to uncontrolled, systemic T-cell activation leading to fatal CRS (80). The cell dose administered to this patient (78) is one hundred times the maximum tolerated dose later found for CD19-CAR T cells (21). In addition, the patient received exogenous IL2, itself associated with high levels of toxicity (81).
Consistent with CRS were dramatic elevations in circulating IFNγ levels. Moreover, Ahmed and colleagues have since used escalating doses of HER2-CD28–ζ CAR T cells to treat patients with sarcomas and demonstrated both safety and initial signs of clinical efficacy, including a CR in a patient with rhabdomyosarcoma in his bone marrow (82, 83). Together, the clinical experience is most consistent with a model whereby differential expression of the HER2 target antigen between tumor and normal tissues provides a therapeutic window for safety, which is consistent with the emerging understanding of the need for high antigen density for optimal CAR activity in vivo.

OVERCOMING LOW ANTIGEN DENSITY

For appropriate targets where the differential expression of target antigen between tumor and normal tissue is high, we predict that the efficacy of CAR therapies would be enhanced by engineering CAR T cells to respond to lower antigen densities. One approach would be to treat patients with agents that increase expression of the target antigen. In preclinical studies, this approach has been taken using all-trans retinoic acid to increase expression of folate receptor beta in AML (84), and researchers at the NCI have found that bryostatin can increase expression of CD22 on leukemia cells, which could lead to increased efficacy of the CD22 CAR or prevention of outgrowth of CD22-low variants (85, 86).

Alternatively, CAR engineering could be used to enhance activity against lower antigen densities. The most commonly attempted modification has been to enhance the affinity of the scFv for its target. For some CARs, it appears that altering the affinity can result in recognition of lower levels of target antigen. Two groups have demonstrated that altering the affinity of EGFR and/or HER2 CARs can result in T cells that are more or less likely to recognize lower levels of antigen as might be expressed on normal tissue (87, 88); however, it remains unclear whether the impact of enhancing scFv activity plateaus. This is suggested by the fact that increasing the affinity of two different CD22 CARs did not result in enhanced function (63, 85).

CONCLUSION

Clinical experience with B-cell malignancies has demonstrated that CAR T cells have the potential to alter the landscape of cancer immunotherapy. However, the emergence of antigen-negative and antigen-low tumor variants has shown that, like all anticancer agents, CARs are likely to require combinatorial approaches to bring about cures in a high fraction of patients. Whereas in hematologic malignancies, lineage-derived antigens are expressed at high levels and can be efficiently targeted by CARs, in solid tumors most viable antigens are expressed at lower levels and more heterogeneously. Reengineering CARs for multispecificity and activity at lower levels of antigen will be an area of important research as the community attempts to enhance the potency of CAR T cells and the breadth of diseases for which they can provide clinically meaningful effects.

Disclosure of Potential Conflicts of Interest

C.L. Mackall reports receiving commercial research grants from Bluebird Bio and Obsidian, has ownership interest (including stock, patents, etc.) in Juno Therapeutics, and is a consultant/advisory board member for Unum Therapeutics, Adaptimmune, GlaxoSmithKline, Vor Pharmaceuticals, Allogene, and NCarta Therapeutics. No potential conflicts of interest were disclosed by the other author.

Acknowledgments

This work was supported by a SU2C-St. Baldrick’s Pediatric Cancer Dream Team Translational Research Grant (SU2CAACR-DT1113). Stand Up To Cancer (SU2C) is a program of the Entertainment Industry Foundation administered by the American Association for Cancer Research. C.L. Mackall is a member of the Parker Institute for Cancer Immunotherapy, which supports the Stanford University Cancer Immunotherapy Program. R.G. Majzner is supported by a Hyundai Hope on Wheels Young Investigator Award and a SARC Career Development Award.

Received April 23, 2018; revised June 22, 2018; accepted July 12, 2018; published first August 22, 2018.

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