Kite Pharma

KITE : NASDAQ : US$36.16

BUY

Target: US$42.00

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COMPANY STATISTICS:

Forecast Return:	16.2%
Shares Out (M):	43.6
Market Cap (M):	US$1,576.6
52-week Range:	21.00 - 36.41
Avg. Daily Vol. (000s):	523.0

EARNINGS SUMMARY:

FYE Dec		2013A	2014E	2015E
Revenue (M):		0.0	0.0	0.0
EPS:		(1.42)	(1.85)	(1.49)
Revenue (M):	Q1	0.0	0.0A	0.0
	Q2	0.0	0.0A	0.0
	Q3	0.0	0.0	0.0
	Q4	0.0	0.0	0.0
Total		0.0	0.0	0.0
EPS:	Q1	--	(0.66)A	(0.38)
	Q2	--	(2.27)A	(0.37)
	Q3	--	(0.28)	(0.37)
	Q4	--	(0.28)	(0.36)
Total		(1.42)	(1.85)	(1.49)

SHARE PRICE PERFORMANCE:

Source: Interactive Data Corporation

COMPANY DESCRIPTION:
Kite Pharma is a clinical-stage biotechnology company incorporated in June 2009 focused on the development of novel cancer immunotherapy using engineered autologous cell therapy (eACT). The technology genetically modifies T-cells to express chimeric antigen receptors (CAR) or T-cell receptors (TCR) which can specifically recognize and destroy the cancer cells.

All amounts in US$ unless otherwise noted.

Life Sciences -- Biotechnology

KITE CHANGES HEMATOLOGIC LANDSCAPE; INITIATE WITH BUY, $42 TARGET

Investment highlights

Novel cellular therapy for lymphoma may change the landscape of personalized medicine

Kite Pharma is at the forefront of a new technology called chimeric antigen receptor T-cell (CART) therapy that has produced stunning efficacy in serious hematological cancers, which we believe will result in substantial long-term value for investors. Early work in conjunction with NCI, positive preliminary phase 1 results, and a large target patient population should position Kite for both near- and long-term success.

Estimate $1.3B US peak sales for CAR-T, DLBCL key

Kite's leading drug candidate KTE-C19 may peak at $1.3B in the US, with diffuse large B-cell lymphoma (DLBCL) being the largest opportunity, peaking at $691M. Assuming continued positive data for KTE-C19, the drug could expand into additional hematological malignancies, offering upside to our peak sales estimates.

Early data ground breaking, 92% ORR with lasting remissions

Early NCI results for KTE-C19 in B-cell malignancies are quite remarkable with an ORR of 92%. Out of the 7 patients with DLBCL, 4 patients achieved CR (57%). We expect Kite to initiate a phase 1/2 trial in DLBCL during Q4/14 based on promising data from an ongoing NCI anti-CD19 CAR T-cell study, with data surfacing during 2H15.

Establishing $42 price target, potential upside to $129

We are establishing a $42 price target based on a probability-adjusted net present valuation. We conservatively assume only a ~30% probability of approval based on current data, with upside to ~$129 if KTE-C19 is approved by FDA. We utilize an effective discount rate of ~11%, which we view as appropriate for a company in the early stages of clinical development.

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INVESTMENT THESIS

We are initiating coverage of Kite Pharma (KITE) with a BUY rating and $42 target price. We believe Kite's main drug KTE-C19 is positioned for success based on the unique technology of modified CAR T-cell therapy for relapsed/refractory hematologic malignancies, specifically in DLBCL. By targeting CD19, an antigen present in most liquid cancers but not on healthy cells, KTE-C19 can elicit a potent and specific anticancer response mediated by a patient's own immune system. The current data on CAR T-cell therapies, presented from various institutions including MSKCC, UPenn, NCI, and Fred Hutchinson Cancer Center, has been extremely positive. CAR T technology has already shown ORR of >80% and CR >50% in various hematologic cancers, versus <40% chance of response for current therapies. KITE is trying to obtain FDA approval for KTE-C19 in DLBCL, which we believe represents more of the potential CAR T-cell therapy patient population than ALL, CLL, FL, and MCL combined. After the DLBCL program, Kite will start clinical trials in the other hematologic disease states to eventually cover all B-cell malignancies.

The CAR T-cell technology being developed by Kite represents a potential paradigm shift in treating hematological cancers, which should result in substantial financial upside for investors. We view the CAR T-cell technology in a similar way as the entry of targeted antibody therapies in the early 1990s. However, CAR T-cell therapy is the first technology to harness the power of the body's own immune system other than IL-2. We believe that the magnitude of therapeutic benefit offered by KTE-C19 will offer a major advance in transforming hematological cancers into chronic diseases and substantially extend patient survival.

Though the risk of toxicity in this therapy should not be overlooked, we believe the use for this therapy is an area of significant unmet need with no effective treatment. Patients with relapsed/refractory DLBCL after second-line therapy, with or without autologous stem cell transplant, have dismal prognosis. Preliminary reports from NCI's data have been impressive. ORR has been as high as 92%, with 57% CR rates and an ongoing duration of 22 months in one patient. Interestingly, patients with bulky disease also responded to CAR T-cell therapy, a limitation previously thought to constrain the effectiveness of this technology in DLBCL compared to ALL. Currently, Kite has not started their own CAR T-cell therapy, but is using the exact same construct and technology as NCI through their CRADA agreement. Based on these positive outcome results from NCI, Kite plans to jumpstart its own clinical trial with a planned IND filing as early as Q4/14.

Similar to most oncology companies, Kite is positioned to realize substantial operating leverage if its KTE-C19 therapy is successful. We anticipate a small salesforce capable of covering the majority of oncology centers treating hematological cancers. Since KTE-C19 is a complicated therapy, we do not anticipate community centers administering their therapy to a large extent, which reduces the size of the required salesforce. Also, nearly every indication that Kite is pursuing is an orphan indication, carrying substantial pricing power. Because of the dramatic response rates seen with KTE-C19, especially in bridging patients to transplant, we believe Kite will have strong leverage in terms of pricing discussions with payors assuming FDA approval.

KTE-C19 is a personalized therapy, with complex manufacturing, providing an extremely high barrier to entry for potential competitors. We would envision a very long revenue tail for KTE-C19 and expect patents to be extremely difficult to circumvent as well as challenge under current FDA framework for biologic drugs. Effectively, we believe that the risk of long-term generic competition is very low, allowing for long-term continued cash flows to be realized.

VALUATION

We are establishing a $42 price target based on a probability-adjusted net present value analysis for KTE-C19. We project peak sales of $1.3B for KTE-C19 in the US by 2020 in DLBCL and sum of the other four different indications in the US by 2021. Outside the US, we assume Kite secures a commercial partner and receives a royalty in Ex-US sales. Our Ex-US peak royalty estimate is ~$99M by 2020. We include: Diffuse Large B-Cell Lymphoma (DLBCL), Chronic Lymphocytic Leukemia (CLL), Acute Lymphoid Leukemia (ALL), Follicular Lymphoma (FL), and Mantle Cell Lymphoma (MCL). Although Kite is pursuing DLBCL as the main indication, we included these other malignancies based on possible off label use by physicians. Also, assuming successful results from the ongoing NCI and company sponsored trials in DLBCL, Kite plans to develop and seek regulatory approval of this therapy for CLL, ALL, FL, and MCL in the upcoming future.

We project peak sales for KTE-C19 based on a detailed model of the US and ex-US market in these hematologic malignancies. We evaluated KTE-C19 in only third-line setting for DLBCL, CLL, FL, MCL and second-line setting for ALL. We project net revenues and apply relevant costs including cost of goods sold (COGS), which we conservatively estimate at ~23% based on ~18% COGS + discounts and rebates and a 5% royalty on net sales to NIH, and a 77.5% gross margin.

Figure 1: Kite valuation

Product	Peak Sales/Royalty ($MM)	Year	NPV at launch	Estimated launch	Time to launch	Probability Adjustment	Current Value ($MM)	Value / Share
KTE-C19								
US								
DLBCL US	$691	2020	$2,970	10/1/2017	2.9	30%	$654	$17
CLL US	$83	2021	$327	10/1/2018	3.9	30%	$65	$2
ALL US	$195	2021	$979	10/1/2018	3.9	30%	$194	$5
FL US	$165	2021	$736	10/1/2018	3.9	30%	$146	$4
MCL US	$164	2021	$732	10/2/2018	3.9	30%	$145	$4
US - total	**$1,298**	**2020**	**$5,744**	**10/1/2017**	**2.9**	30%	**$1,266**	**$33**
Ex-US								
DLBCL royalty Ex-US	$53	2020	$508	6/1/2018	3.6	30%	$104	$3
CLL royalty Ex-US	$6	2021	$56	6/1/2019	4.6	30%	$10	$0
ALL royalty Ex-US	$15	2021	$142	6/1/2019	4.6	30%	$26	$1
FL royalty Ex-US	$13	2021	$110	6/2/2019	4.6	30%	$20	$1
MCL royalty Ex-US	$12	2021	$109	6/3/2019	4.6	30%	$20	$1
Ex-US - royalty - total	**$99**	**2020**	**$994**	**6/1/2018**	**3.6**	30%	**$204**	**$5**
Total Product Value							**$1,409**	**$37**
Cash							$200	$5.3
Total Equity Value							**$1,609**	**$42**
Shares Outstanding (MM)							38	

Risk-Free Rate	3.0%
Beta	1.8
Risk Premium	5%
Discount Rate	11%

Source: Canaccord Genuity estimates, company reports

From the gross margins, we subtract R&D and SG&A costs to arrive at operating profit and assume taxes at a rate of ~37% ~2 years after potential FDA approval to arrive at net profit. We discount net profit back to the launch date at a rate of 11%, and then probability-adjust it by 30%.

We assume potential FDA approval for KTE-C19 in 2017. We then discount back to the present at 11% to arrive at an NPV. We also used a terminal value in 2025 which assumes minimal generic risk for this immunotherapy. The effective discount rate, taking into account our 30% probability adjustment is 23%.

We assume Kite partners its therapy in the EU, with a royalty of ~20%. The net royalty is 15% after a 5% royalty to NIH.

Our valuation is probability adjusted by 30% for KTE-C19. Historical data shows that drugs in phase 1 have a 15-20% chance of FDA approval. Although Kite has not started its own clinical trial yet, the current success of NIH's phase 1 CAR T-cell therapy is used as a basis of our assumption since the license to NIH's technology is held under their CRADA agreement. In addition, we believe these indications represent an area of unmet need with no viable treatment options. Kite currently has orphan drug designation to KTE-C19, furthering a positive FDA filing. Therefore, our model gives a potential valuation of $42.

CATALYSTS

Anticipate IND filing to start phase 1-2 KTE-C19 trial Q4/14

We expect IND filing and approval to initiate KITE's own CAR T-cell clinical trial for DLBCL in Q4/14 based on recent promising clinical results from NCI's phase 1-2a trial. This will be a phase 1-2 single-arm multicenter clinical trial of KTE-C19 in patients with DLBCL who have failed two or more lines of therapy. Due to the current positive interim results from NCI's phase 1-2a clinical trial, we view a year-end IND filing and patient enrollment starting 1H15 as a positive.

KTE-C19 preliminary data from phase 1-2 trial expected YE15

We anticipate positive preliminary data similar to the results seen in NCI's current phase 1-2a, possibly presented at ASH 2015. Importantly, we do not believe that Kite will need to generate overall survival data given the very high response rates seen in the previous phase 1 trial in DLBCL. Assuming Kite generates a similar Complete Response rate seen in the NIH study, we believe shares will appreciate significantly.

Expect accelerated approval 2016 if phase 1-2 trial positive

Assuming positive data, Kite plans to file a BLA for accelerated approval of KTE-C19 as third-line therapy for DLBCL. We would expect FDA to grant the accelerated approval given the strong unmet medical need for third-line DLBCL patients combined with the very strong clinical results to date for KTE-C19. For example, data from the NCI study showed significant lymphoma reduction in one patient's liver after failing 10 prior regimens, and near resolution of lymph node mass in a CLL patient.

Expect to file IND relating to a TCR-based and EGFRvIII CART product candidate YE15

Kite plans to exclusively license and develop a portfolio of TCR-based product candidates targeting various cancers based on data from the NCI phase 2 clinical trial, which could lead to further upside for the stock. We view this as a positive combination with the current KTE-C19 product. TCR-based product candidates target specific antigens expressed by cancer cells irrespective of where the cancer originates, potentially useful target for solid tumors. In addition, Kite is currently funding an NCI phase 1-2a clinical trial of CAR-based T-cell therapy targeting EGVFvIII antigen in patients with glioblastoma. If results show positive, we expect Kite to file IND for this therapy as well, creating further upside to the stock since no options exist for glioblastoma besides bevacizumab, which has shown only moderate benefit.

Figure 2: Kite catalysts

Event	Timing	Description	Effect	Importance	Notes
CART	4Q14	IND filing	↑	Critical	Expect IND approval to initiate Phase 1-2 single-arm in DLBCL pts who failed 2 or more therapies
CART	4Q14	KTE-C19 in DLBCL update	↑	Critical	ASH Update expected
CART	1-2Q15	Patient enrollment of Phase 1-2 trial	↑	Critical	Expect enrollment to complete by 1Q16
CART	YE15	Preliminary data from phase 1-2 trial	↑	Critical	Possibly ASCO or ASH
CART	YE15	BLA - Accelerated approval if phase 1-2 trial positive	↑	Critical	Based on surrogate or intermediate clinical endpoints, including tumor shrinkage
CART	2016	Randomized trial as 2nd line for DLBCL	↑	Critical	Captures additional patient population of ~2000 patients
TCR	YE15	IND filing	↑	Moderate	Dependent on candidate per CRADA
EGFRvIII	2016	IND filing	↑	Moderate	Neuroblastoma

Source: Canaccord Genuity, company reports

COMPANY OVERVIEW

Kite Pharma is a clinical-stage biotechnology company incorporated in June 2009 focused on the development of novel cancer immunotherapy using engineered autologous cell therapy (eACT). The technology genetically modifies T-cells to express chimeric antigen receptors (CAR) or T-cell receptors (TCR) which can specifically recognize and destroy the cancer cells. Kite is working in collaboration with NCI where under the CRADA agreement, the company holds the option to negotiate commercialization licenses from the NIH to intellectual property relating to CAR and TCR products developed in the course of the CRADA research plan. This includes the right to negotiate a license to IP for drug candidates that are being tested in multiple phase 1-2a clinical trials by NIH and funded by Kite. These candidates not only include antigens expressed in only hematologic malignancies (CD19), but also in epithelial cancers including SSX2, NY-ESO-1, MAGE and EGFRvIII. The CRADA has a five-year term expiring on August 30, 2017. Currently, the company is funding a phase 2 clinical trial of a TCR-based product candidate along with the multiple CAR based product candidates. Although the NCI already filed the investigational new drug applications (INDs) with the FDA, Kite must submit separate INDs to conduct their own trials relating to these product candidates. While funding the NCI trial pursuant to the CRADA agreement, Kite does not expect to license intellectual property relating to KTE-C19 from the NIH. In addition, the company is planning to build its own internal research and development capabilities to explore the next-generation eACT technology.

The company also holds an exclusive, worldwide license agreement with Cabaret Biotech Ltd surrounding intellectual property and licenses by Cabaret relating to CAR constructs that encompass KTE-C19.

The product under development is KTE-C19, a CAR-based therapy, in patients with relapsed/refractory diffuse large B-cell lymphoma (DLBCL). KTE-C19 will use the identical anti-CD19 CAR construct and viral vector that is being used in the NCI trial, but with a more streamlined manufacturing process compared to NCI. The company is currently funding NCI's phase 2 clinical trial of TCR-based therapy and multiple phase 1-2a clinical trials of CAR- and TCR- based therapies. In an ongoing clinical trial, patients with relapsed/refractory lymphomas and leukemia's treated with CAR-based therapy experienced an objective response rate of 92%. Seven of these patients had DLBCL with a complete response seen in four patients, lasting from nine to 22 months.

The company plans to conduct its own phase 1-2 clinical trial in 2015 for KTE-C19 in relapsed/refractory DLBCL with a separate IND from NCI. If data remains compelling, Kite will attempt to file a BLA for accelerated approval of KTE-C19 as third-line therapy for DLBCL. Kite will also plan to initiate a randomized study in 2016 for KTE-C19 as second-line treatment for DLBCL, as well as other hematologic malignancies including CLL, ALL, FL, and MCL. In addition, the company is also seeking to develop additional CAR and TCR based product candidates, specifically CAR-T targeting the EGFRvIII antigen in patients with glioblastoma, and also solid tumors.

Kite plans to commercialize its CAR T-cell product KTE-C19 due the modest salesforce requirements and very high operating margins potentially associated with the product.

Kite believes to have optimized the NCI's manufacturing process of CAR T-cells for their KTE-C19 product. The small number of large hematology cancer centers combined with few patients being treated by community oncologists should allow for success. We currently expect the company to partner in the EU for commercialization of KTE-C19.

RISKS TO OUR OUTLOOK

Although NCI is conducting a phase 1-2a trial of anti-CD19 CAR T-cell therapy, KITE's KTE-C19 trial has not begun. Any delays or significant negative results from NCI's clinical trials could negatively affect Kite's IND application and delay the timing to start its own phase 1-2 clinical trial. In addition, despite similar constructs with the NCI CAR T-cell therapy, the FDA may not allow Kite to use the NCI clinical trial data to support its own IND if demonstration of comparability of KITE's eACT cannot be identified with NCI's model. Although Kite has a CRADA agreement with NIH to negotiate commercialization licenses from the NIH, there is no assurance that Kite would be able to successfully complete such negotiations

KITE is highly dependent on the third parties for R&D and early clinical testing of CAR and TCR product candidates. These collaborations related to the intellectual property licensed from the NIH relating to product candidates targeting the EGFRvIII antigen, the SSX2 antigen and the NY-ESO-1 antigen and from Cabaret for intellectual property relating to KTE-C19. Additionally, Kite does not own any facility or processing facility, relying on outside vendors to manufacture supplies. If these third parties terminate the collaboration agreement for clinical testing/R&D and fail to meet deadlines, the valuation can be negatively affected.

The differences in manufacturing compared to NCI may render the product incomparable, particularly with respect to clinical trials, which could negatively affect our valuation. Although plans for manufacturing and processing is based on current approach undertaken by the NCI, the company cannot ensure that even minor changes in the product process will not result in significantly different T-cells that may not have similar efficacy or toxicity.

KTE-C19 could fail in clinical studies, resulting in significant downside to our price target and shares of the stock. Unlike the high complete response rates seen in acute lymphoblastic leukemia (83% CR), DLBCL may not respond as well to this technology due to the different microenvironment between the two diseases. Also, the TCR technology may not perform as well in solid tumors as in hematological malignancies, resulting in downside to the stock. Although we do not include any revenues in our model or valuation for solid tumors, investors may be disappointed in potentially negative results in solid tumors, pressuring the share price.

The risk of serious side effects, particularly the cytokine storm in which mortality has already been reported, may significantly limit the product use by physicians and result in the downside of the stock. This also can cause regulatory authorities to interrupt or delay clinical trials, which can lead to the possible delay or regulatory denial by the FDA. Also, long-term data on the safety of CAR T-cell therapy is not yet available. CAR T-cells use a retroviral vector to genetically modify normal T-cells. This retroviral vector is known to have some non-specificity with respect to integration. There remains a possibility that

non-specific integration may cause serious safety issues over the long-term, which could results in KTE-C19 being permanently withdrawn from the market.

Kite faces significant competition from other biotechnology and pharmaceutical companies in the space of immunotherapy, including Novartis, Juno, Bluebird, Cellectis and Adaptimmune, as well as companies developing novel targeted therapies for cancer. In particular, Novartis and Juno Therapeutics are in the process of research and development of their own version of an anti-CD19 CAR T-cell therapy, while Adaptimmune plans to compete with any TCR-based product candidates that KITE develops. Cellectis is also pursuing allogeneic T-cell products that could compete with eACT. Any advancement in these companies will negatively affect KITE's market share opportunity and decrease our valuation.

CHIMERIC ANTIGEN RECEPTOR T-CELL DRUG COULD PEAK AT >$1B

KTE-C19 is a novel shift in the way physicians treats hematologic malignancies when current therapies are ineffective. Therefore, Kite has leverage in negotiating costs with payers due to the unmet need of these indications. Although Kite is going after DLBCL as primary indication, company guidance has reported that they will initiate KTE-C19 trials soon in CLL, ALL, FL, and MCL.

ESTIMATE $691M US PEAK BY 2020 IN DLBCL ALONE

We model $691M for US peak sales of KTE-C19 by 2020, based on a detailed revenue build tied to data from the Surveillance, Epidemiology, and End Results (SEER) program. We estimate the incidence of DLBCL in the US at ~27,000 patients total by 2020, where nearly all patients will need initial therapy after diagnosis. We initially separate the market by early stage (stage I-II) and late stage (stage III-IV) patients, since response rates to chemotherapy vary by the stage of disease. SEER report a total of ~17,000 patients with stage I-II disease. According to the MINT trial, response rates in these patients are ~85% and PFS ~80% in 6 years. Therefore, ~2,500 patients will be refractory to first line therapy and ~1,000 patients will eventually relapse, totaling ~3,500 patients requiring second-line therapy. For late stage disease (stage III-IV), SEER data projects ~13,000 patients in total. Although the response rates are still ~80%, the PFS drops to ~55%, based on data from RCHOP 14 vs. RCHOP 21 in late stage DLBCL showing 3 year PFS of 55%. Therefore, we project ~2,500 patients will be refractory to first line chemotherapy and ~2,000 patients will relapse, totaling ~4,500 patients combined. In total, we estimate a total of **~8,000 patients will need second-line therapy**.

For second-line patients, we divided the treatment group to patients' eligible to autologous stem cell transplant (autoSCT) vs. non-eligible patients. Because most DLBCL patients are elderly, we estimate only ~25% are transplant eligible. Therefore, only ~2,000 patients are eligible for autoSCT and ~6,000 patients are ineligible. In the autoSCT eligible patients, response rates have been reported to be ~65% (with the DHAP regimen), and 1-2 year PFS of ~46% according to the PARMA study. Therefore, we project that ~700 patients will be refractory to second-line autoSCT therapy and another ~700 patients will relapse, totaling ~1,400 patients. For the ~6,000 patients ineligible for

autoSCT, the response rates to second-line chemotherapy are reduced to ~45% (reported from the BR regimen) and PFS is only 20%, with a time to relapse of about 1.5 years. Therefore, we estimate ~3,000 patients to be refractory to second-line therapy and ~1,500 patients will relapse, totaling ~4,500 patients.

Altogether, we estimate **~6,000 patients will need third-line chemotherapy** (~1,400 patients from autoSCT eligible and ~4,500 patients from autoSCT ineligible). With a market share of 55% (~3,300 patients) and an annual cost of ~$200,000/patient, we project US revenues ~$691M.

Figure 3: US KTE-C19 DLBCL revenue build

	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E
US DLBCL - Incidence	**26,855**	**24,105**	**24,708**	**25,326**	**25,959**	**26,608**	**27,273**	**27,955**	**28,653**	**29,370**	**30,104**	**30,857**
Market												
Stage I-II total	14,502	14,792	15,145	15,507	15,878	16,257	16,646	17,044	17,451	17,869	18,296	18,734
Stage III-IV total	12,353	12,600	12,852	12,852	12,852	12,852	12,852	13,109	13,109	13,109	13,109	13,109
2nd line	7,444	7,593	7,757	7,832	7,908	7,987	8,067	8,242	8,326	8,412	8,501	8,591
3rd line	5,724	5,838	5,964	6,022	6,081	6,141	6,203	6,337	6,402	6,468	6,536	6,606
Treated Patients												
First line	26,855	24,105	24,708	25,326	25,959	26,608	27,273	27,955	28,653	29,370	30,104	30,857
2nd line												
AutoSCT eligible	1,861	1,898	1,939	1,958	1,977	1,997	2,017	2,060	2,082	2,103	2,125	2,148
Not AutoSCT eligible	5,583	5,695	5,818	5,874	5,931	5,990	6,050	6,181	6,245	6,309	6,375	6,443
3rd line	5,724	5,838	5,964	6,022	6,081	6,141	6,203	6,337	6,402	6,468	6,536	6,606
Market Share												
First line	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
2nd line AutoSCT eligible	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
2nd line not Auto SCT eligible	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
3rd line	0%	0%	0%	25%	50%	55%	55%	55%	55%	55%	55%	55%
Total CART	**-**	**-**	**-**	**1,505**	**3,040**	**3,377.53**	**3,411**	**3,485**	**3,521**	**3,558**	**3,595**	**3,633**
First line	-	-	-	-	-	-	-	-	-	-	-	-
2nd line AutoSCT eligible	-	-	-	-	-	-	-	-	-	-	-	-
2nd line Not AutoSCT eligible	-	-	-	-	-	-	-	-	-	-	-	-
3rd line	-	-	-	1,505	3,040	3,378	3,411	3,485	3,521	3,558	3,595	3,633
Cost per patient				**$ 175,000**	**$ 183,750**	**$ 192,938**	**$ 202,584**	**$ 212,714**	**$ 223,349**	**$ 234,517**	**$ 246,243**	**$ 258,555**
US DLBCL CART Annual Revenue ($000)	**-**	**-**	**-**	**$ 263,453**	**$ 558,660**	**$ 651,652**	**$ 691,116**	**$ 741,395**	**$ 786,421**	**$ 834,297**	**$ 885,212**	**$ 939,364**

Source: Canaccord Genuity estimates, Company reports, SEER Database

CLL MAY PEAK AT $83M IN US

We estimate ~$83M peak US sales in the CLL landscape by 2021. We assume 2021 because the company plans to start clinical trials in other hematologic malignancies in 2015, one year after the start of DLBCL trials. SEER data estimates ~18,000 patients with CLL by 2021. We separated the patient population by early RAI stage (0-2) and late stage (3-4) disease, with ~13,000 patients and ~5,000 patients, respectively. Because CLL is an indolent disease, patients in early stage are not treated with chemotherapy. However, this disease is not curable and patients will eventually progress to late stage disease, requiring chemotherapy. We estimate 60% of patients will progress to late stage disease, totaling about ~8,000 patients. For late stage disease, SEER data estimate

~4,000 patients that require treatment. Therefore, we estimate a total of **~12,000 patients eligible for first line chemotherapy**.

Out of the ~12,000 patients requiring treatment, we next divided the market into younger patients (~45%, ~5,500 patients) and older patients (~55%, ~6,500 patients) since most patients are diagnosed at a later age. Although NCCN state that 66% of CLL patients are >70 years old, we estimated ~55% because there are patients above the age of 70 that are "fit" for intense chemotherapy. In the ~5,500 younger patient subgroup, the overall response rates reported with intensive chemotherapy regimens, including PCR, FCR, or BR, is ~95% with 4-5 year median PFS of 50%. Therefore, we project only ~1,000 patients will require second-line therapy. Older patients (~6,500 patients) who cannot tolerate intensive chemotherapy can still obtain an ORR of 80% with first line single agent fludarabine. However, nearly all patients will relapse, with 1.5 year PFS of only 20%. We project ~1,500 elderly patients will be refractory to front therapy, and ~4,500 will relapse, totaling ~6,000 patients. Therefore, we estimate a total of **~7,000 patients will be relapsed/refractory, requiring second-line therapy**.

For the ~7,000 relapsed/refractory patients, second-line therapy would be intensive chemotherapy for younger patients again and single agent chemotherapy for older patients. However, the development of P13K and BTK inhibitors changed the landscape of disease treatment in the relapsed/refractory setting. Now, response rates have been as high as ~90% with 2-3 year PFS of 75%. Given these high response rates and durable remissions, we estimate only **~1,000-1,300 patients in both young and elderly patients requiring third-line agents**. We believe KTE-C19 will only be used in this patient population initially. We give 30% market share (~300-400 patients total) and an annual cost of ~$200,000/patient, we project US revenues for CLL patients to be ~$83M.

Figure 4: US KTE-C19 CLL revenue build

	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E
US CLL - Incidence	**15,564**	**15,875**	**16,192**	**16,516**	**16,847**	**17,183**	**17,527**	**17,878**	**18,235**	**18,600**	**18,972**	**19,351**
Market												
Stage 0-2	11,673	11,906	12,144	12,387	12,635	12,888	13,145	13,408	13,676	13,950	14,229	14,514
Stage 3-4	3,891	3,969	4,048	4,129	4,212	4,296	4,382	4,469	4,559	4,650	4,743	4,838
1st line	10,895	11,112	11,335	11,561	11,793	12,028	12,269	12,514	12,765	13,020	13,280	13,546
2nd line	5,861	5,978	6,097	6,219	6,344	6,471	6,600	6,732	6,867	7,004	7,144	7,287
3rd line	1,132	1,155	1,178	1,201	1,225	1,250	1,275	1,300	1,326	1,353	1,380	1,408
Patients treated												
1st line												
Young patients	4,903	5,001	5,101	5,203	5,307	5,413	5,521	5,631	5,744	5,859	5,976	6,096
Old patients	5,992	6,112	6,234	6,359	6,486	6,616	6,748	6,883	7,021	7,161	7,304	7,450
2nd line												
Young patients	827	844	861	878	895	913	932	950	969	989	1,008	1,029
Old patients	5,033	5,134	5,237	5,341	5,448	5,557	5,668	5,782	5,897	6,015	6,136	6,258
3rd line	1,132	1,155	1,178	1,201	1,225	1,250	1,275	1,300	1,326	1,353	1,380	1,408
Market Share												
1st line young patients	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
1st line old patients	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
2nd line young patients	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
2nd line old patients	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
3rd line	0%	0%	0%	0%	15%	30%	30%	30%	30%	30%	30%	30%
Total CART	**-**	**-**	**-**	**-**	**183.8**	**375.0**	**382.5**	**390.1**	**397.9**	**405.9**	**414.0**	**422.3**
1st line young patients	-	-	-	-	-	-	-	-	-	-	-	-
1st line old patients	-	-	-	-	-	-	-	-	-	-	-	-
2nd line young patients	-	-	-	-	-	-	-	-	-	-	-	-
2nd line old patients	-	-	-	-	-	-	-	-	-	-	-	-
3rd line	-	-	-	-	184	375	382	390	398	406	414	422
Cost per patient					**$ 183,750**	**$ 192,938**	**$ 202,584**	**$ 212,714**	**$ 223,349**	**$ 234,517**	**$ 246,243**	**$ 258,555**
US CLL CART Annual Revenue ($000s)	**-**	**-**	**-**	**$ 33,776**	**$ 72,349**	**$ 77,486**	**$ 82,987**	**$ 88,879**	**$ 95,190**	**$ 101,948**	**$ 109,186**	

Source: Canaccord Genuity estimates, Company reports, SEER Database

ALL ADDS ~$195M US PEAK

SEER data estimates an incidence of ~8,000 patients with ALL by 2021. Not only is ALL a very heterogeneous malignancy, the relapse rate and prognosis of these patients are strongly affected by the age of the patient. Therefore, we separated the market into three age tiers in accordance with NCCN recommendations: 1) pediatric and adolescents <25 years old (~5,000 patients), 2) young adults 25-39 year olds (~700 patients), and 3) adults of >40 years old (~2,500 patients). The problem with ALL is not the response rates, since most patients are able to obtain good CR with initial therapy. However, these patients have a short duration of response, and most patients eventually relapse. Once patients relapse, the CR rates significantly decreases from ~85% in first line to 30-40% in relapse disease. Additionally, patients that do achieve CR will most likely go to allogeneic stem cell transplant as this is the only potential cure after relapse.

For pediatric and adolescents, current regimens like NYII can achieve a high response rate of ~95% with 4 year PFS of as high as 80%. Therefore, we project ~250 patients who will be refractory to initial induction therapy and only another ~500 patients who will relapse, totaling ~750 patients. Once patients are relapsed/refractory to initial treatment, pediatric and adolescent patients have a 40-50% CR to second induction chemotherapy,

leaving **~450 patients going to allogeneic transplant and ~300 patients requiring third-line therapy**.

For young adults, current regimens, including ALL-2, HyperCVAD, and ECOG2993 can also achieve a high response rate of ~90% with 4 year PFS of 65-80%. Therefore, out of the total ~700 patients, we project ~70 patients who will be refractory to initial induction therapy and only another ~60 patients who will relapse, totaling ~130 patients. Once patients are relapsed/refractory to initial treatment, these patients have a 40-50% CR to second induction chemotherapy, leaving **~60 patients requiring allogeneic transplant and ~60 patients needing third-line chemotherapy**.

Finally, adult patients usually have poor prognosis compared to younger patients. Although these patients can achieve high CR rates of ~85%, only 60% of patients achieve PFS at 3 years. Out of the ~2,500 patients, we estimate ~400 patients will be refractory to first line therapy and ~500 patients will relapse, totaling ~900 patients that require second-line therapy. Here, the CR with relapse disease is only 30%, with nearly everyone relapsing within 5-6 months. Therefore, out of the 900 patients requiring second-line agent, we estimate **~350 patients will require allogeneic transplant and ~550 patients will need third-line therapy**.

Combining the total number of patients, we estimate ~800 patients (~450 pediatric, ~60 young adults, and ~350 adults) will receive allogeneic transplant after second-line therapy and ~900 patients (~300 pediatrics, ~60 young adults, and ~550 adults) with third-line chemotherapy. We give 25% market share (~200 patients) for KTE-C19 for the transplant group since these patients already can achieve CR prior to alloSCT with conventional chemotherapy, while we give 75% market share (~700 patients) to the third-line chemotherapy group since these patients will probably not respond to the treatment. This totals to about **900 patients per year eligible for KTE-C19**. Applying a cost of ~$200,000 per patient, we estimate an annual revenue of ~$195M.

Figure 5: US KTE-C19 ALL revenue build

	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E
US ALL - Incidence	**6198**	**6508**	**6833**	**7175**	**7534**	**7910**	**8306**	**8721**	**9157**	**9615**	**10096**	**10600**
Market												
<25 year old	3722	3908	4103	4308	4524	4750	4987	5237	5499	5774	6062	6365
25-39	512	537	564	592	622	653	686	720	756	794	834	875
>40	1964	2063	2166	2274	2388	2507	2632	2764	2902	3047	3200	3360
2nd line <25 yrs old	540	567	595	625	656	689	723	759	797	837	879	923
2nd line 25-39	97	102	107	113	118	124	130	137	144	151	158	166
2nd line >40	629	660	693	728	764	802	842	885	929	975	1024	1075
Treated Patients												
<25 first line	3722	3908	4103	4308	4524	4750	4987	5237	5499	5774	6062	6365
<25 second line												
Transplant	297	312	327	344	361	379	398	418	439	460	483	508
Non-transplant	243	255	268	281	295	310	325	342	359	377	396	415
25-39 first line	512	537	564	592	622	653	686	720	756	794	834	875
25-39 second line												
Transplant	49	51	54	56	59	62	65	68	72	75	79	83
Non-transplant	49	51	54	56	59	62	65	68	72	75	79	83
>40 first line	1964	2063	2166	2274	2388	2507	2632	2764	2902	3047	3200	3360
>40 second line												
Transplant	251	264	277	291	306	321	337	354	371	390	410	430
Non-transplant	377	396	416	437	458	481	505	531	557	585	614	645
Market Share												
<25 first line	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**
<25 second line - transplant	**0%**	**0%**	**0%**	**0%**	**10%**	**25%**	**25%**	**25%**	**25%**	**25%**	**25%**	**25%**
<25 second line - nontransplan	**0%**	**0%**	**0%**	**0%**	**35%**	**75%**	**75%**	**75%**	**75%**	**75%**	**75%**	**75%**
25-39 first line	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**
25-39 second line - transplant	**0%**	**0%**	**0%**	**0%**	**10%**	**25%**	**25%**	**25%**	**25%**	**25%**	**25%**	**25%**
25-39 second line - nontranspl	**0%**	**0%**	**0%**	**0%**	**35%**	**75%**	**75%**	**75%**	**75%**	**75%**	**75%**	**75%**
>40 first line	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**	**0%**
>40 second line - transplant	**0%**	**0%**	**0%**	**0%**	**10%**	**25%**	**25%**	**25%**	**25%**	**25%**	**25%**	**25%**
>40 second line - nontransplan	**0%**	**0%**	**0%**	**0%**	**35%**	**75%**	**75%**	**75%**	**75%**	**75%**	**75%**	**75%**
Total CART patients	**-**	**-**	**-**	**-**	**357**	**830**	**871.98**	**915.58**	**961**	**1,009**	**1,060**	**1,113**
<25 first line	-	-	-	-	-	-	-	-	-	-	-	-
<25 second line - transplant	-	-	-	-	36	95	99	104	110	115	121	127
<25 second line - nontransplan	-	-	-	-	103	232	244	256	269	283	297	312
25-39 first line	-	-	-	-	-	-	-	-	-	-	-	-
25-39 second line - transplant	-	-	-	-	6	16	16	17	18	19	20	21
25-39 second line - nontranspl	-	-	-	-	21	47	49	51	54	57	59	62
>40 first line	-	-	-	-	-	-	-	-	-	-	-	-
>40 second line - transplant	-	-	-	-	31	80	84	88	93	98	102	108
>40 second line - nontransplan	-	-	-	-	160	361	379	398	418	439	461	484
Cost per patient					**$ 183,750**	**$ 192,938**	**$ 202,584**	**$ 212,714**	**$ 223,349**	**$ 234,517**	**$ 246,243**	**$ 258,555**
US ALL CART Annual Revenue ($000)	**-**	**-**	**-**	**-**	**$ 65,599**	**$ 160,226**	**$ 176,649**	**$ 194,756**	**$ 214,718**	**$ 236,727**	**$ 260,991**	**$ 287,743**

Source: Canaccord Genuity estimates, Company reports, SEER database

FOLLICULAR LYMPHOMA ESTIMATE $165M SALES

We estimate peak US sales of $165M for FL based on SEER data estimate, with a total incidence of ~17,000 patients and prevalence of ~100,000 patients with FL by 2021. Because this is a very indolent disease, ~20% of patients do not need treatment as physicians "watch and wait" for disease progression, leaving us with **~13,000 patients requiring front-line therapy**. We divided the market into ~4,000 early stage (I-II) patients and ~9,000 late stage (III-IV) patients. For early stage disease, chemotherapy plus radiation has been shown to have an ORR of 80% and relapse on average of ~8 years,

leaving us with ~1,000 patients. In late stage disease, RCHOP therapy has been shown to also have a high ORR of ~90%. However, these patients have a much shorter remission, where nearly all patients relapse about 2.5 years, yielding total of ~4,000 patients requiring second-line therapy. Consequently, from incidence alone, we obtain ~5,000 patients that are relapsed/refractory to front-line FL therapy. Because FL is such an indolent disease, it is important to take into account the ~100,000 patients with FL from prevalence. Therefore, we multiplied the prevalence data by 2 to get a total of **~10,000 patients requiring second-line therapy**. We cross referenced this data with epidemiology various epidemiology studies (SEET, Mattson Jack TA data, Q1 2012 rituxan tracking, IARC scientific publications No. 160), which reported a total of ~11,000 FL patients treated for relapsed/refractory disease in 2012.

For second-line treatment in the ~11,000 relapsed/refractory FL patients, RCHOP therapy has been shown to produce an ORR of ~80%. Patients can still maintain a long remission duration once they relapse/refractory to initial chemotherapy, especially with autoSCT where the PFS is reported to be ~30% in 3 years. Therefore, we estimate ~2,000 patients will be refractory to second-line therapy and ~500 patients will relapse per year, totaling **~2,500 patients requiring third-line therapy**. We give 30% market share (~750 patients) and an annual cost of ~$200,000/patient, we project US revenues for FL patients to be ~$165M.

Figure 6: US KTE-C19 FL revenue build

	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E
US Follicular - Incidence	15846	**16163**	**16325**	**16488**	**16653**	**16820**	**16988**	**17158**	**17329**	**17503**	**17678**	**17854**
Market												
Stage I	2561	2612	2638	2665	2691	2718	2745	2773	2801	2829	2857	2886
Stage IE	160	163	165	167	168	170	172	173	175	177	179	180
Stage II	1761	1796	1814	1832	1850	1869	1888	1906	1925	1945	1964	1984
Stage IIE	640	653	660	666	673	680	686	693	700	707	714	721
Stage III	2561	2612	2638	2665	2691	2718	2745	2773	2801	2829	2857	2886
Stage IV	8163	8327	8410	8494	8579	8665	8751	8839	8927	9016	9107	9198
Treated patients												
First line	12165	12408	12532	12658	12784	12912	13041	13172	13303	13436	13571	13706
Stage I-II	3585	3657	3694	3731	3768	3806	3844	3882	3921	3960	4000	4040
Stage III-IV	8579	8751	8839	8927	9016	9106	9197	9289	9382	9476	9571	9667
Second line	9355	9542	9637	9734	9831	9929	10029	10129	10230	10333	10436	10540
Third line	2387	2435	2459	2484	2509	2534	2559	2585	2611	2637	2663	2690
Market share												
First line	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
2nd line	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
3rd line	0%	0%	0%	0%	15%	30%	30%	30%	30%	30%	30%	30%
Total CART patients	-	-	-	-	**376**	**760**	**768**	**775**	**783**	**791**	**799**	**807**
First line	-	-	-	-	-	-	-	-	-	-	-	-
2nd line	-	-	-	-	-	-	-	-	-	-	-	-
3rd line	-	-	-	-	376	760	768	775	783	791	799	807
Cost per patient					$ 183,750	$ 192,938	$ 202,584	$ 212,714	$ 223,349	$ 234,517	$ 246,243	$ 258,555
US FL CART Annual Revenue ($000)				$ -	$ 69,152	$ 146,671	$ 155,545	$ 164,955	$ 174,935	$ 185,518	$ 196,742	$ 208,645

Source: Canaccord Genuity estimates, Company reports, SEER database

ADDITIONAL $164M FROM MANTLE CELL LYMPHOMA

We estimate ~$164M peak US sales in the MCL landscape by 2021. MCL makes up only a small proportion of all NHL, though it is characterized as a very aggressive disease state. SEER data estimates an incidence of about **~3,500 patients with MCL by 2021 where all patients will require initial therapy upon diagnosis**. In this disease, although ORR can be high of 80%, CR rate is only 60% with traditional chemotherapy. Due to the aggressive nature of the malignancy, PFS has been reported to be only 35% at 1 year. Therefore, we estimate that ~1,350 patients will be refractory to initial therapy and ~1,350 patients will relapse, totaling ~2,700 patients requiring second-line therapy.

Unfortunately, most patients with MCL that require second-line therapy have a poor prognosis. Even with ibrutinib, with an ORR of ~67%, the average PFS is only ~ 1 year, with 50% overall survival at 18 months. Therefore, we estimate ~800 patients that are refractory to second-line therapy and ~1,700 patients that will relapse within one year, totaling **~2,500 patients needing third-line agent**. Again, we give 30% market share (~750 patients) and an annual cost of ~$200,000/patient, projecting US revenues for MCL patients to be ~$164M.

Figure 7: US KTE-C19 MCL revenue build

	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E
US Mantle Cell Lymphoma	3208	3287	3320	3353	3386	3420	3454	3489	3524	3559	3595	3631
Market												
Stage I	308	316	319	322	325	329	332	335	339	342	345	349
Stage IE	92	95	96	97	98	99	100	101	102	103	104	105
Stage II	185	189	191	193	195	197	199	201	203	205	207	209
Stage IIE	31	32	32	32	33	33	33	34	34	34	35	35
Stage III	277	284	287	290	293	296	299	302	305	308	311	314
Stage IV	2314	2371	2395	2419	2443	2467	2492	2517	2542	2568	2593	2619
Treated patients												
First line	3208	3287	3320	3353	3386	3420	3454	3489	3524	3559	3595	3631
Second line	2534	2597	2623	2649	2675	2702	2729	2756	2784	2812	2840	2868
Third line	2365	2423	2447	2471	2496	2521	2546	2572	2597	2623	2650	2676
Market share												
First line	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
2nd line	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
3rd line	0%	0%	0%	0%	15%	30%	30%	30%	30%	30%	30%	30%
Total CART patients	-	-	-	-	374	756	764	771	779	787	795	803
First line	-	-	-	-	-	-	-	-	-	-	-	-
Second line	-	-	-	-	-	-	-	-	-	-	-	-
Third line	-	-	-	-	374	756	764	771	779	787	795	803
Cost per patient					$ 183,750	$ 192,938	$ 202,584	$ 212,714	$ 223,349	$ 234,517	$ 246,243	$ 258,555
US MCL CART Annual Revenue ($000)				$ -	$ 68,796	$ 145,916	$ 154,744	$ 164,106	$ 174,034	$ 184,564	$ 195,730	$ 207,571

Source: Canaccord Genuity estimates, Company reports, SEER database

EX-US ROYALTIES ~$99M PEAK

We estimate $90M in Ex-US royalties by 2020-2021, with $53M in DLBCL (2020), $6M in CLL, $15M in ALL, $13M in FL, and $12M in MCL. Although the market population is larger ex-US (we estimated 50% more than US for all disease state), we used the same clinical assumptions for each disease state to get the ~11,000 patients for DLBCL, ~1,900 patients for CLL, ~2,500 patients for ALL, ~3,900 patients for FL, and ~4,000 patients for MCL eligible for CAR T-cell therapy. Additionally, we used the same assumption of market share for each individual disease, though we believe it will take an additional year to reach the assumed market share. Therefore, total patients for KTE-C19 is ~4,900 patients for DLBCL, ~600 patients for CLL, ~1,300 patients for ALL, 1,200 patients for FL, and 1,100 patients for MCL. For pricing, we assumed a fix cost of 65% of US cost, averaging $113,750 per patient. Therefore, we estimate annual revenue of ~$560M for DLBCL, $65M for CLL, $150M for ALL, $131M for FL, and $130M for MCL. Assuming 20% royalty to KITE and 5% of KITE's royalty goes to NIH, we estimate $53M in DLBCL, $6M in CLL, $15M in ALL, $13M in FL, and $12M in MCL, totaling $99M by 2020-2021.

Figure 8: Ex-US KTE-C19 DLBCL revenue build

	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E
EU DLBCL - Incidence	**46,997**	**42,184**	**43,239**	**44,320**	**45,428**	**46,563**	**47,727**	**48,921**	**50,144**	**51,397**	**52,682**	**53,999**
Market												
Stage I-II total	25,378	25,886	26,504	27,137	27,786	28,450	29,130	29,827	30,540	31,270	32,018	32,784
Stage III-IV total	21,618	22,051	22,492	22,492	22,492	22,492	22,492	22,942	22,942	22,942	22,942	22,942
2nd line	13,027	13,288	13,575	13,705	13,839	13,977	14,117	14,423	14,571	14,722	14,876	15,034
3rd line	10,017	10,217	10,437	10,538	10,641	10,747	10,855	11,090	11,203	11,319	11,438	11,560
Treated Patients												
First line	46,997	42,184	43,239	44,320	45,428	46,563	47,727	48,921	50,144	51,397	52,682	53,999
2nd line												
AutoSCT eligible	3,257	3,322	3,394	3,426	3,460	3,494	3,529	3,606	3,643	3,680	3,719	3,759
Not AutoSCT eligible	9,771	9,966	10,181	10,279	10,380	10,483	10,588	10,817	10,928	11,041	11,157	11,276
3rd line	10,017	10,217	10,437	10,538	10,641	10,747	10,855	11,090	11,203	11,319	11,438	11,560
Market Share												
First line	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
2nd line AutoSCT eligible	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
2nd line not Auto SCT eligible	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
% Share CART				15%	30%	40%	45%	50%	55%	55%	55%	55%
Total CART	-	-	-	**1,581**	**3,192**	**4,299**	**4,885**	**5,545**	**6,162**	**6,226**	**6,291**	**6,358**
First line	-	-	-	-	-	-	-	-	-	-	-	-
2nd line AutoSCT eligible	-	-	-	-	-	-	-	-	-	-	-	-
2nd line Not AutoSCT eligible	-	-	-	-	-	-	-	-	-	-	-	-
3rd line	-	-	-	1,581	3,192	4,299	4,885	5,545	6,162	6,226	6,291	6,358
Cost per patient				**$ 113,750**	**$ 113,750**	**$ 113,750**	**$ 113,750**	**$ 113,750**	**$ 113,750**	**$ 113,750**	**$ 113,750**	**$ 113,750**
EU DLBCL CART Annual Revenue ($000)	**-**	**-**	**-**	**$ 179,806**	**$ 363,129**	**$ 488,974**	**$ 555,628**	**$ 630,741**	**$ 700,906**	**$ 708,168**	**$ 715,605**	**$ 723,221**
EU Royality to Kite				20%	20%	20%	20%	20%	20%	20%	20%	20%
KITE royality to NCI				5%	5%	5%	5%	5%	5%	5%	5%	5%
Tax - 37%				37%	37%	37%	37%	37%	37%	37%	37%	37%
Net EU DLBCL Revenue ($000)				**$ 16,992**	**$ 34,316**	**$ 46,208**	**$ 52,507**	**$ 59,605**	**$ 66,236**	**$ 66,922**	**$ 67,625**	**$ 68,344**

Source: Canaccord Genuity estimates, Company reports, SEER Database

Figure 9: Ex-US KTE-C19 CLL revenue build

	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E
EU CLL - Incidence	**23,345**	**23,812**	**24,289**	**24,774**	**25,270**	**25,775**	**26,291**	**26,816**	**27,353**	**27,900**	**28,458**	**29,027**
Market												
Stage 0-2	17,509	17,859	18,216	18,581	18,952	19,331	19,718	20,112	20,515	20,925	21,343	21,770
Stage 3-4	5,836	5,953	6,072	6,194	6,317	6,444	6,573	6,704	6,838	6,975	7,114	7,257
1st line	16,342	16,669	17,002	17,342	17,689	18,043	18,403	18,772	19,147	19,530	19,921	20,319
2nd line	8,791	8,967	9,146	9,329	9,515	9,706	9,900	10,098	10,300	10,506	10,716	10,930
3rd line	1,698	1,732	1,767	1,802	1,838	1,875	1,912	1,951	1,990	2,029	2,070	2,111
Treated Patients												
1st line												
Young patients	7,354	7,501	7,651	7,804	7,960	8,119	8,282	8,447	8,616	8,788	8,964	9,144
Old patients	8,988	9,168	9,351	9,538	9,729	9,923	10,122	10,324	10,531	10,741	10,956	11,175
2nd line												
Young patients	1,241	1,266	1,291	1,317	1,343	1,370	1,398	1,425	1,454	1,483	1,513	1,543
Old patients	7,550	7,701	7,855	8,012	8,172	8,336	8,502	8,672	8,846	9,023	9,203	9,387
3rd line	1,698	1,732	1,767	1,802	1,838	1,875	1,912	1,951	1,990	2,029	2,070	2,111
Market Share												
1st line young patients	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
1st line old patients	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
2nd line young patients	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
2nd line old patients	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
3rd line	0%	0%	0%	0%	10%	20%	30%	30%	30%	30%	30%	30%
Total CART	**-**	**-**	**-**	**-**	**184**	**375**	**574**	**585**	**597**	**609**	**621**	**633**
1st line young patients	-	-	-	-	-	-	-	-	-	-	-	-
1st line old patients	-	-	-	-	-	-	-	-	-	-	-	-
2nd line young patients	-	-	-	-	-	-	-	-	-	-	-	-
2nd line old patients	-	-	-	-	-	-	-	-	-	-	-	-
3rd line	-	-	-	-	184	375	574	585	597	609	621	633
Cost per patient				**$ 113,750**	**$ 113,750**	**$ 113,750**	**$ 113,750**	**$ 113,750**	**$ 113,750**	**$ 113,750**	**$ 113,750**	**$ 113,750**
EU CLL CART Annual Revenue ($000)	**-**	**-**	**-**	**-**	**$ 20,909**	**$ 42,655**	**$ 65,262**	**$ 66,567**	**$ 67,898**	**$ 69,256**	**$ 70,641**	**$ 72,054**
EU Royality to Kite					20%	20%	20%	20%	20%	20%	20%	20%
KITE royality to NCI					5%	5%	5%	5%	5%	5%	5%	5%
Tax - 37%					37%	37%	37%	37%	37%	37%	37%	37%
Net EU CLL Revenue ($000)					**$ 1,976**	**$ 4,031**	**$ 6,167**	**$ 6,291**	**$ 6,416**	**$ 6,545**	**$ 6,676**	**$ 6,809**

Source: Canaccord Genuity estimates, Company reports, SEER Database

Figure 10: Ex-US KTE-C19 ALL Revenue Build

	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E
EU ALL - Incidence	**9297**	**9762**	**10250**	**10762**	**11300**	**11865**	**12459**	**13081**	**13736**	**14422**	**15143**	**15901**
Market												
<25 year old	5582	5862	6155	6462	6786	7125	7481	7855	8248	8660	9093	9548
25-39	768	806	846	889	933	980	1029	1080	1134	1191	1250	1313
>40	2947	3094	3249	3411	3582	3761	3949	4146	4353	4571	4800	5040
<25 year old	5582	5862	6155	6462	6786	7125	7481	7855	8248	8660	9093	9548
2nd line <25 yrs old	**809**	**850**	**892**	**937**	**984**	**1033**	**1085**	**1139**	**1196**	**1256**	**1319**	**1384**
2nd line 25-39	**146**	**153**	**161**	**169**	**177**	**186**	**195**	**205**	**216**	**226**	**238**	**249**
2nd line >40	**943**	**990**	**1040**	**1092**	**1146**	**1203**	**1264**	**1327**	**1393**	**1463**	**1536**	**1613**
Treated Patients												
<25 first line	5582	5862	6155	6462	6786	7125	7481	7855	8248	8660	9093	9548
<25 second line												
Transplant	445	467	491	515	541	568	597	626	658	691	725	761
Non-transplant	364	382	402	422	443	465	488	513	538	565	593	623
25-39 first line	768	806	846	889	933	980	1029	1080	1134	1191	1250	1313
25-39 second line												
Transplant	73	77	80	84	89	93	98	103	108	113	119	125
Non-transplant	73	77	80	84	89	93	98	103	108	113	119	125
>40 first line	2947	3094	3249	3411	3582	3761	3949	4146	4353	4571	4800	5040
>40 second line												
Transplant	377	396	416	437	458	481	505	531	557	585	614	645
Non-transplant	566	594	624	655	688	722	758	796	836	878	922	968
Market Share												
<25 first line	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
<25 second line - transplant	0%	0%	0%	0%	10%	18%	25%	25%	25%	25%	25%	25%
<25 second line - nontransplan	0%	0%	0%	0%	25%	50%	75%	75%	75%	75%	75%	75%
25-39 first line	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
25-39 second line - transplant	0%	0%	0%	0%	10%	18%	25%	25%	25%	25%	25%	25%
25-39 second line - nontranspl	0%	0%	0%	0%	25%	50%	75%	75%	75%	75%	75%	75%
>40 first line	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
>40 second line - transplant	0%	0%	0%	0%	10%	18%	25%	25%	25%	25%	25%	25%
>40 second line - nontransplan	0%	0%	0%	0%	25%	50%	75%	75%	75%	75%	75%	75%
Total CART patients	**-**	**-**	**-**	**-**	**414**	**846**	**1,308**	**1,373**	**1,442**	**1,514**	**1,590**	**1,669**
<25 first line	-	-	-	-	-	-	-	-	-	-	-	-
<25 second line - transplant	-	-	-	-	54	102	149	157	164	173	181	190
<25 second line - nontransplan	-	-	-	-	111	232	366	384	404	424	445	467
25-39 first line	-	-	-	-	-	-	-	-	-	-	-	-
25-39 second line - transplant	-	-	-	-	9	17	24	26	27	28	30	31
25-39 second line - nontranspl	-	-	-	-	22	47	73	77	81	85	89	94
>40 first line	-	-	-	-	-	-	-	-	-	-	-	-
>40 second line - transplant	-	-	-	-	46	87	126	133	139	146	154	161
>40 second line - nontransplan	-	-	-	-	172	361	569	597	627	658	691	726
Cost per patient			**$**	**113,750**	**$**	**113,750**	**$**	**113,750**	**$**	**113,750**	**$**	**113,750**	**$**	**113,750**	**$**	**113,750**	**$**	**113,750**	**$**	**113,750**
EU ALL CART Annual Revenue ($000)			**$**	**-**	**$**	**47,046**	**$**	**96,197**	**$**	**148,781**	**$**	**156,220**	**$**	**164,031**	**$**	**172,233**	**$**	**180,845**	**$**	**189,887**
EU Royality to Kite					20%	20%	20%	20%	20%	20%	20%	20%
KITE royality to NCI					5%	5%	5%	5%	5%	5%	5%	5%
Tax - 37%					37%	37%	37%	37%	37%	37%	37%	37%
Net EU ALL Revenue ($000)				**-**	**$**	**4,446**	**$**	**9,091**	**$**	**14,060**	**$**	**14,763**	**$**	**15,501**	**$**	**16,276**	**$**	**17,090**	**$**	**17,944**

Source: Canaccord Genuity estimates, Company reports, SEER Database

Figure 11: Ex-US KTE-C19 FL revenue build

	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E
EU Follicular - Incidence	23769	24245	24487	24732	24980	25229	25482	25736	25994	26254	26516	26781
Market												
Stage I	3841	3918	3958	3997	4037	4077	4118	4159	4201	4243	4285	4328
Stage IE	240	245	247	250	252	255	257	260	263	265	268	271
Stage II	2641	2694	2721	2748	2776	2803	2831	2860	2888	2917	2946	2976
Stage IIE	960	980	989	999	1009	1019	1030	1040	1050	1061	1071	1082
Stage III	3841	3918	3958	3997	4037	4077	4118	4159	4201	4243	4285	4328
Stage IV	12245	12490	12615	12741	12868	12997	13127	13258	13391	13525	13660	13797
Treated patients												
First line	18247	18612	18798	18986	19176	19368	19562	19757	19955	20154	20356	20560
Second line	14032	14313	14456	14601	14747	14894	15043	15194	15346	15499	15654	15810
Third line	3581	3653	3689	3726	3763	3801	3839	3877	3916	3955	3995	4035
Market share												
First line	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
2nd line	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
3rd line	0%	0%	0%	0%	10%	20%	30%	30%	30%	30%	30%	30%
Total CART patients	-	-	-	-	376	760	1,152	1,163	1,175	1,187	1,198	1,210
First line	-	-	-	-	-	-	-	-	-	-	-	-
2nd line	-	-	-	-	-	-	-	-	-	-	-	-
3rd line	-	-	-	-	376	760	1,152	1,163	1,175	1,187	1,198	1,210
Cost per patient				$ 113,750	$ 113,750	$ 113,750	$ 113,750	$ 113,750	$ 113,750	$ 113,750	$ 113,750	$ 113,750
EU FL CART Annual Revenue				$ -	$ 42,808	$ 86,473	$ 131,006	$ 132,316	$ 133,639	$ 134,976	$ 136,326	$ 137,689
EU Royality to Kite				20%	20%	20%	20%	20%	20%	20%	20%	20%
KITE royality to NCI				5%	5%	5%	5%	5%	5%	5%	5%	5%
Tax - 37%				37%	37%	37%	37%	37%	37%	37%	37%	37%
Net EU FL Revenue ($000)				-	$ 4,045	$ 8,172	$ 12,380	$ 12,504	$ 12,629	$ 12,755	$ 12,883	$ 13,012

Source: Canaccord Genuity estimates, Company reports, SEER database

Figure 12: Ex-US KTE-C19 MCL revenue build

	2014E	2015E	2016E	2017E	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E
EU Mantle Cell Lymphoma	4812	4930	4979	5029	5080	5130	5182	5233	5286	5339	5392	5446
Market												
Stage I	462	474	478	483	488	493	498	503	508	513	518	523
Stage IE	139	142	144	145	146	148	149	151	152	154	155	157
Stage II	277	284	287	290	293	296	299	302	305	308	311	314
Stage IIE	46	47	48	48	49	49	50	50	51	51	52	52
Stage III	416	426	431	435	439	444	448	452	457	462	466	471
Stage IV	3472	3557	3592	3628	3665	3701	3738	3776	3813	3851	3890	3929
Treated patients												
First line	4812	4930	4979	5029	5080	5130	5182	5233	5286	5339	5392	5446
Second line	3802	3895	3934	3973	4013	4053	4094	4134	4176	4218	4260	4302
Third line	3547	3634	3670	3707	3744	3781	3819	3857	3896	3935	3974	4014
Market share												
First line	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
2nd line	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
3rd line	0%	0%	0%	0%	10%	20%	30%	30%	30%	30%	30%	30%
Total CART patients	-	-	-	-	374	756	1,146	1,157	1,169	1,180	1,192	1,204
First line	-	-	-	-	-	-	-	-	-	-	-	-
Second line	-	-	-	-	-	-	-	-	-	-	-	-
Third line	-	-	-	-	374	756	1,146	1,157	1,169	1,180	1,192	1,204
Cost per patient				$ 113,750	$ 113,750	$ 113,750	$ 113,750	$ 113,750	$ 113,750	$ 113,750	$ 113,750	$ 113,750
EU MCL CART Annual Revenue ($000)				$ -	$ 42,588	$ 86,028	$ 130,332	$ 131,635	$ 132,952	$ 134,281	$ 135,624	$ 136,980
EU Royality to Kite					20%	20%	20%	20%	20%	20%	20%	20%
KITE royality to NCI					5%	5%	5%	5%	5%	5%	5%	5%
Tax - 37%					37%	37%	37%	37%	37%	37%	37%	37%
Net EU MCL Revenue ($000)				-	$ 4,025	$ 8,130	$ 12,316	$ 12,440	$ 12,564	$ 12,690	$ 12,816	$ 12,945

Source: Canaccord Genuity estimates, Company reports, SEER database

CART CLINICAL RESULTS UNPRECEDENTED IN LYMPHOMAS, LEUKEMIAS

Highlights from pivotal CAR T-cell clinical trial in DLBCL (Kochenderfer J. *JCO* 2014)

- 12/13 patients with advanced B-cell malignancy – 92% ORR (61% CR; 31% PR)
- In DLBCL patients 4/7 CR (57%); 2/7 PR (29%); 1/7 SD (14%)
- Duration of response: 9-22 months
- Reversible toxicities – fever, hypotension, delirium, neurologic toxicity

NCI SHOWS POSITIVE RESPONSE IN DLBCL

Under Kite's CRADA agreement, advancements in NCI clinical trials should be viewed as a positive for Kite's stock price. Interesting data has been reported in patients with aggressive Non-Hodgkin's lymphoma currently on NCI's anti-CD19 CAR T-cell clinical trial, which we feel will be a move forward for the company to file an IND in the fourth quarter of this year to initiate its own phase 1-2 clinical trial. NCI is currently enrolling in

3 clinical trials to date including both pediatric and adult B-cell malignancies and adults with B-cell malignancies who relapsed post allogeneic stem cell transplant. We remind investors that Kite is currently targeting for FDA approval in DLBCL and is the only company in the CAR T-cell space to report trial results (NCI) in DLBCL.

Figure 13: Current clinical trials for NCI with CAR T-cell therapy

Cancers	Title	Trial	Inclusion	Study Arm	Primary Endpoints	Secondary Endpoints
All CD19 B-cell malignancy	Phase I study of B cell Malignancies Using T cells expressing an Anti-CD19 Chimeric Recepor: Assessment of the Impact of Lymphocyte Depletion of the Impact of Lymphocyte Depletion Prior to T-cell transfer	Phase I NCT00924326 Start Feb 2009 Estimate enroll 40 pts Estimate completion - 1/2017	CLL/MCL/FL must have PD or SR after 1 tx CLL pts must have received ibrutinib Large cell lymphoma must have PD or SD after at least 2 tx Relapsed/refractory ALL s/p 1 tx ECOG 0-1; life expectancy > 3 months	Single Arm (Excludes prior transplant)	Safety and feasibility	In vivo survival of CAR-T cells Regression of B-cell malignancies
	Anti-CD19 WBC for children and young adults with B-cell leukemia or lymphoma	Phase I NCT01593696 Start 2012 Estimate enroll 48 Estimate completion - 1/2020	ALL, B-cell lymphoma, leukemia, large cell, NHL Children and young adults between 1 - 30 years	2 arms 1 - Prior allo SCT 2 - No SCT	Safety and feasibility	In vivo survival of CAR-T cells Regression of B-cell malignancies
	Administration of Anti-CD19-chimeric-antigen-receptor-transduced T Cells From the Original Transplant Donor to Patients With Recurrent or Persistent B-cell Malignancies After Allogeneic Stem Cell Transplantation	Phase 1 NCT01087294 Start Feb 2010 Estimate enroll - 36 pts Estimate completion - 1/2015	18 - 75 yo pts who have received alloSCT for a B-cell cancer without response. Recipients must have the same stem cell donor from previous procedure ECOG < or equal to 2	2 Arms 1 - Dose escalation of Matched sibs 2 - Dose escalation of unrelated	Safety and feasibility	none

Source: Clinicaltrials.gov

The trial generating current interest is highlighted above, with interim reports recently reported. Up to this point, 9 patients with DLBCL and 6 patients with indolent B-cell malignancies have been treated; however, 1 patient died soon after treatment, and one patient was lost to follow-up because of non-compliance. 13 patients with advanced, heavily pretreated (2-12 prior regimens) B-cell malignancies were treated with 1-5 x 106 CAR-positive T-cells/kg. All patients received conditioning chemotherapy of cyclophosphamide 60 or 120 mg/kg, followed by five daily doses of fludarabine 25 mg/m2 to deplete endogenous leukocytes prior to CAR T-cell administration. Patients did not receive exogenous IL-2.

Of the 12 out of 13 advanced B-cell malignancies, 8 patients had CR (61%) and 4 patients had PR (31%), resulting in a 92% ORR. The table below shows that most of these patients were heavily pretreated and refractory to prior regimens. Of the seven evaluable patients with chemotherapy-refractory DLBCL, age adjusted risk factors include 6 patients with high risk, 1 patient with intermediate risk, and 1 patient with low risk disease. The results showed impressive response rates in these 7 DLBCL patients with 4 CRs (57%), 2 PRs (29%), and 1 stable disease (14%). This is a significant step forward because current therapies for this patient population have response rates of only <40% with CRs <20% historically. Three of the patients with CRs continue to have ongoing remissions, ranging from 9 to 22 months. Due to this long duration, a critical unanswered question remains

as to whether any of the CRs achieved in this trial will lead to permanent progression free survival.

Figure 14: Patient baseline characteristics of CAR T-cell therapy in DLBCL

Table 1. Patient Clinical Characteristics

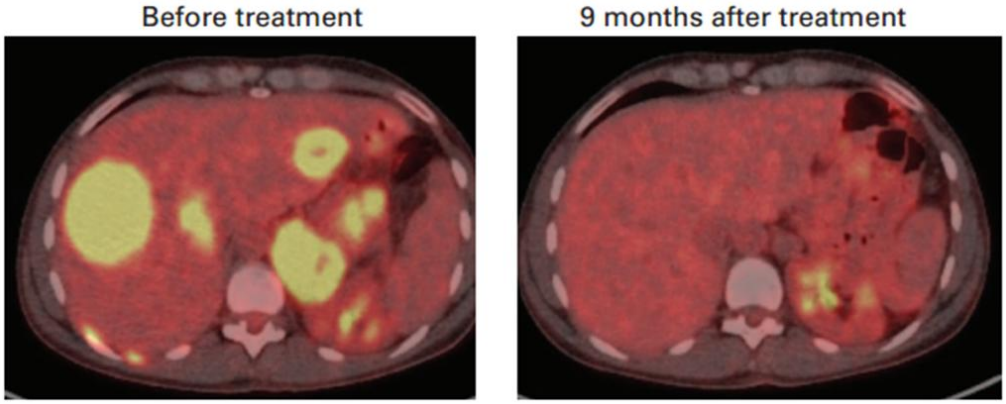
Patient No.	Age (years)	Sex	Malignancy	No. of Prior Therapies[a]	sAAIPI Risk Group	Total Cyclophosphamide Dose (mg/kg)[b]	No. of CAR-Positive T Cells Infused (× 10^6/kg)	Response[c]		Grade ≥ 3 Toxicities[d]
								Type	Duration (months)	
1[e]	56	Male	SMZL	4	NA	120	5	PR	23+[f]	Hypotension, confusion, acute renal failure, fever
2	43	Female	PMBCL[g]	4	Low	60	5	CR	22+[f]	Fever, confusion, aphasia, facial nerve palsy, headache, urinary tract infection
3	61	Male	CLL (FR)	2	NA	60	4	CR	23+[f]	Headache, fever, confusion, hypotension
4	30	Female	PMBCL[g]	3	High	120	2.5	NE		Nausea, hypoxia, dyspnea, tachycardia, fever, bacteremia, malaise, vascular leak syndrome, death
5[e]	63	Male	CLL	4	NA	120	2.5	CR	15+[f]	None
6	48	Male	CLL (FR)	1	NA	60	2.5	CR	14+[f]	None
7	42	Male	DLBCL NOS[g]	5	High	60	2.5	CR	9+[f]	Influenza, fever, headache, bacteremia
8	44	Female	PMBCL[g]	10	High	60	2.5	CR	12+[f]	Fever, pneumonitis, hypotension, hypoxia, bacteremia, obtundation, elevated creatinine
9	38	Male	PMBCL[g]	3	High	120	2.5	SD	1	Fever, aphasia, myoclonus
10	57	Female	Low-grade NHL[h]	4	NA	60	1	CR	11+[f]	Bacteremia, fever, fatigue
11	58	Female	DLBCL[g] from CLL	12	High	60	1	PR	1	Bacteremia, urinary tract infection, fever
12	60	Female	DLBCL NOS[g]	3	High	60	1	NE[i]		Fever, urinary tract infection, bacteremia, upper extremity thrombosis
13	68	Male	CLL	4	NA	60	1	PR	4	Dyspnea, upper extremity thrombosis, urinary tract infection, creatinine increase, hypotension
14	43	Male	DLBCL NOS[g]	2	High	60	1	CR	6	Fever
15	64	Female	DLBCL NOS[h]	3	Intermediate	60	1	PR	6+[f]	Fever, aphasia, encephalopathy, neuropathy, gait disturbance

Source: Kochenderfer J et al. *JCO* 2014

Compared with ALL (reported CR rates in the high 80s), data from other institutions show limited response rates in patients with high tumor burden and bulky disease, a common characteristic in DLBCL and CLL. This limitation represents the different microenvironment needed for T-cell survival between ALL and the other hematologic diseases, highlighting the prerequisite for T-cell infiltration in malignant lymph nodes to be effective the treatment of lymphoma. Interestingly, patients with bulky disease still responded favorably to NCI's CAR T-cell therapy. The figure below shows a patient with advanced primary mediastinal B-cell lymphoma with significant burden of disease in her liver and other areas after failing 10 prior regimens. This patient was highly resistant to chemotherapy where progression was seen < 1 month after receiving each of four

different regimens, including R-CHOP, R-ICE, R-high dose cytarabine, and R-GDP. After CAR T-cell, CR was maintained for 12 months.

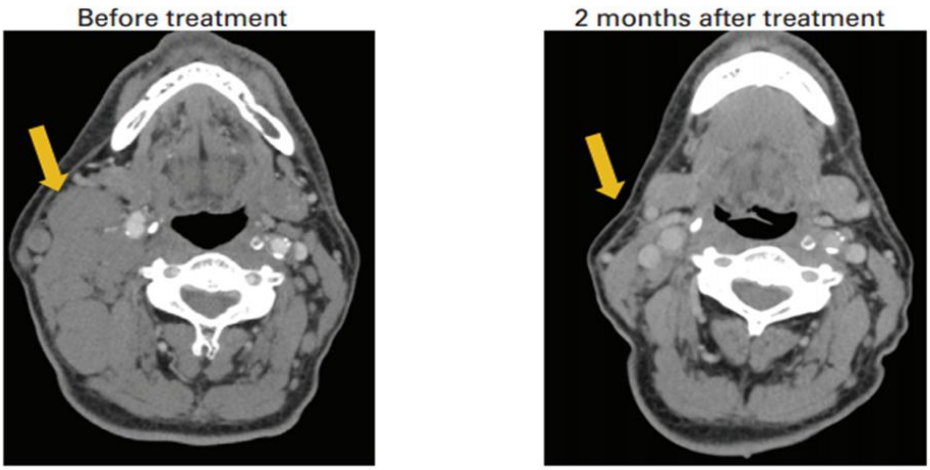
Figure 15: PET/CT image show CR of lymphoma in patient



Source: Kochenderfer J et al. *JCO* 2014

Unlike ALL where effectiveness may be the level of T-cells detected in the serum after therapy, a more important indicator of effectiveness may be the number of CAR-positive T-cells found in lymphoma masses. NCI's CAR T-cells were shown to readily infiltrate malignant lymph nodes, reflected in the patient below with CLL manifesting in part as a bulky cervical lymph node mass. The figure shows the near resolution of a CLL patient after treatment. Fine needle aspiration of the lymph node mass showed continued CAR T-cell uptake, further justifying the ability of the T-cells to infiltrate and treat bulky diseases.

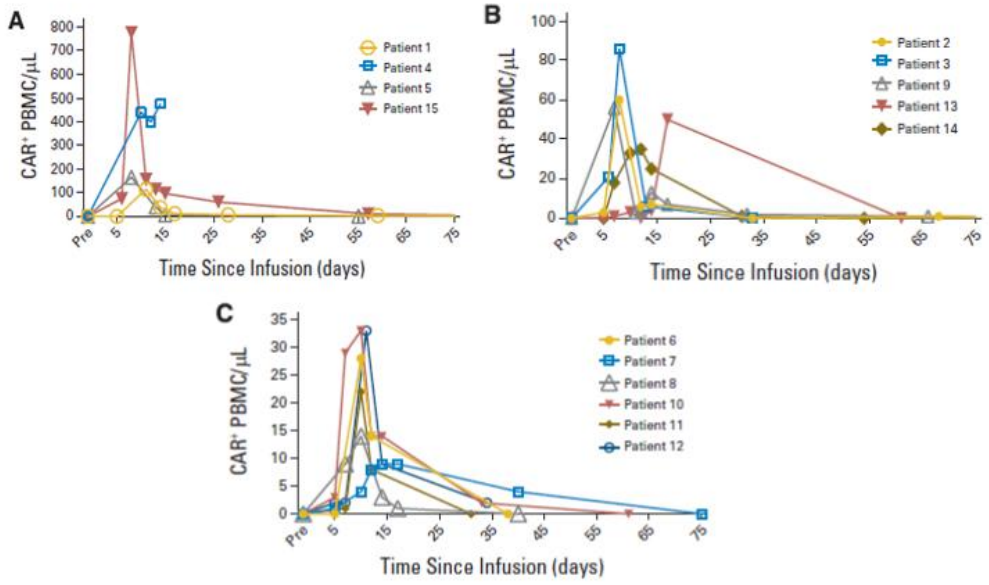
Figure 16: CT scan show regression of large cervical lymph node mass



Source: Kochenderfer J et al. *JCO* 2014

It was noted that CAR T-cells had variable peak blood levels and persistence. PCR measurements show peak levels varied from 9 – 777 CAR-positive cells/uL. The duration of CAR-positive blood cells peaked between 7 and 17 days after infusion. Currently, the importance of detectable CAR T-cells in the serum remains unclear, as many other trials from various institutions report different peak levels and durations. However, data shows high peak levels of CAR T-cells after infusion demonstrates T-cell expansion and proliferation in the body, while persistence in the blood demonstrates sustainability, relating to a possible correlation to better efficacy and longer treatment duration.

Figure 17: Variable levels of anti-CD19 CAR T-cells in blood



Source: Kochenderfer J et al. *JCO* 2014

A possible explanation of the short duration of T-cells in NCI's trial is the differentiation that occurred in CAR T-cells from time to infusion to time of peak blood levels. NCI found a decrease in the percentage of CAR T-cells with a central memory phenotype, mainly found during infusion, to an increase in effector memory phenotype found during peak levels. These phenotypic changes indicate a shift toward a more differentiated T-cell phenotype, partially explaining the rapid decrease of memory T-cells detected in the blood after peak. Therefore, generating CAR T-cells that maintain a less differentiated phenotype might improve the duration of T-cells in the blood and possible efficacy as well.

Infusion of CAR T-cells was associated with significant but transient toxicities. Nearly all patients experienced some degree of transient grade III or IV toxicity. These included fever, hypotension, headache, and infections. Neurologic toxicities were also seen in most patients, including transient aphasias, confusion, obtundation and one person experiencing severe generalized myoclonus which eventually resolved by day 11. Though these results remain troublesome and the mechanism of these neurologic toxicities is not known, it is important to note that all patients recovered completely from their neurologic toxicities.

POSITIVE RESULTS FOUND IN ALL

Highlights from NCI's CAR T-cell clinical trial in ALL (Lee D. *Lancet* 2014)

- 14/20 patients with relapsed/refractory ALL – 70% CR
- Overall survival – 51.6% at 10 months
- 10/12 responders went to bone marrow transplant
- Fully reversible toxicities – cytokine release syndrome grade III-IV – 28%

Figure 18: Current clinical trials for NCI with CAR T-cell therapy

Cancers	Title	Trial	Inclusion	Study Arm	Primary Endpoints	Secondary Endpoints
DLBCL All CD19 B-cell malignancy	Phase I study of B cell Malignancies Using T cells expressing an Anti-CD19 Chimeric Recepor: Assessment of the Impact of Lymphocyte Depletion Prior to T-cell transfer	Phase I NCT00924326 Start Feb 2009 Estimate enroll 40 pts Estimate completion - 1/2017	CLL/MCL/FL must have PD or SR after 1 tx CLL pts must have received ibrutinib Large cell lymphoma must have PD or SD after at least 2 tx Relapsed/refractory ALL s/p 1 tx ECOG 0-1; life expectancy > 3 months	Single Arm (Excludes prior transplant)	Safety and feasibility	In vivo survival of CAR-T cells Regression of B-cell malignancies
	Anti-CD19 WBC for children and young adults with B-cell leukemia or lymphoma	Phase I NCT01593696 Start 2012 Estimate enroll 48 Estimate completion - 1/2020	ALL, B-cell lymphoma, leukemia, large cell, NHL Children and young adults between 1 - 30 years Dose escalation of T-cells (1x10^6; 3x10^6; 1x10^7)	2 arms 1 - Prior allo SCT 2 - No SCT	Safety and feasibility	In vivo survival of CAR-T cells Regression of B-cell malignancies
	Administration of Anti-CD19-chimeric-antigen-receptor-transduced T Cells From the Original Transplant Donor to Patients With Recurrent or Persistent B-cell Malignancies After Allogeneic Stem Cell Transplantation	Phase 1 NCT01087294 Start Feb 2010 Estimate enroll - 36 pts Estimate completion - 1/2015	18 - 75 yo pts who have received alloSCT for a B-cell cancer without response. Recipients must have the same stem cell donor from previous procedure ECOG < or equal to 2 Donor must be same that was originally used	2 Arms 1 - Dose escalation of Matched sibs 2 - Dose escalation of unrelated	Safety and feasibility	none

Source: Clinicaltrials.gov

Phase 1 data for relapsed/refractory ALL patients were recently published in Lancet by the NCI, reporting positive results in this setting. This was a dose-escalation trial evaluating the feasibility, toxicity, maximum tolerated dose, response rate, and biological correlation of CAR T-cells with refractory ALL. All patients received fludarabine and cyclophosphamide before CAR T-cell infusion.

Most patients were heavily pretreated with cytotoxic chemotherapy, including 6 patients with B-ALL who never attained an MRD-negative remission despite many intensive chemotherapy regimens and 8 who had undergone alloSCT. 2 patients had measureable CNS leukemia.

21 patients were enrolled, with 1 patient having DLBCL. The maximum tolerated dose found was 1 x 10^6 cells/kg. The trial reported a CR in 14/20 pediatric or young adult patients (70%) with relapsed/refractory ALL. Overall survival at a median follow up of 10 months was 51.6% at 9.7 months and beyond. 12/20 patients (60%) achieved a minimal residual disease (MRD)-negative complete response, with continued disease free upon 10 months of follow-up. Importantly, because the standard of care for refractory b-ALL patients is bone marrow transplant (HSCT), 10 of the 12 patients who were MRD-negative went on to HSCT and all remained disease free at the 10 month median follow up, concluding this therapy to be a very effective bridge to HSCT.

In terms of toxicities, grade 4 cytokine release syndrome occurred in 14% of patients, grade 3 fever in 43%, hypokalemia in 43%, febrile neutropenia in 38%, and CRS in 14%. Neurotoxicity was seen in 6 patients, though all were transient. Interestingly, all patients with neurotoxicity had evidence of CNS trafficking of CD19 Car T-cells. Anti-interleukin-6 receptor monoclonal antibody tocilizumab was used in 4 patients. All toxicities were fully reversible, demonstrating a positive safety profile.

Figure 19: Baseline characteristics of relapsed/refractory ALL patients

	Age	Sex	Previous treatment	Number of relapses	Marrow blasts (% of mononuclear)		CNS status	CAR dose ($\times 10^6$/kg)	Response (day 28)	CRS grade	Absolute circulating CAR T cells at day 28 ($\times 10^6$/kg)	Days until HSCT after CAR
					Pre-treatment	Post-CAR						
1	13	M	C, R, I, T	8	30%	1%	1	1	CRi	2	1	..
2	16	F	C, R, T	2	35%	40%	1	0·03	SD	0	1·9	..
3	10	F*	C, R, I, T	Primary refractory	..	..	..	1	PD	1	0	..
4	11	F	C	Primary refractory	58%	<0·01%	1	1	CR, MRD Neg	1	2·8	47
5	10	M	C	1	10%	<0·01%	1	0·48	CR, MRD Neg	2	0·4	82
6	10	M	C	3	81%	99%	1	3†	PD	1	0	..
7	25	M	C, I	1	50%	0·03%	1	3	CR	4‡	0	..
8	18	M	C, R, T	1	0·2%	<0·01%	2	1	CR, MRD Neg	1	3	..
9	13	M	C, R, I, T, CAR	3	0·56%	<0·01%	1	3	CR, MRD Neg	1	3·1	45
10	5	M	C	Primary refractory	5%	<0·01%	1	3	CR, MRD Neg	3	0	54
11	23	M	C, R	1	84%	<0·01%	2	1	CR, MRD Neg	3	6·5	54
12	9	M	C	1	95%	96%	1	1	PD	0	0	..
13	27	F	C	3	21%	43%	1	1	PD	0	0	..
14	15	M	C, R, T	3	96%	<0·01%	1	1	CR, MRD Neg	4‡§	1·4	..
15	5	F	C, R, T	1	15%	10%	1	1	SD	0	0	..
16	25	M	C	Primary refractory	50%	<0·01%	1	1	CR, MRD Neg	4‡§	3·1	63
17	18	F	C	Primary refractory	0·03%	<0·01%	1	1	CR, MRD Neg	1	0·2	48
18	13	M	C, R, T	2	90%	97%	1	1	SD	0	0	..
19	21	M	C	2	7·7%	<0·01%	1	1	CR, MRD Neg	3‡	40·3	55
20	16	F	C	Primary refractory	0·7%	<0·01%	1	1	CR, MRD Neg	1	0	46
21	6	M	C	Primary refractory	0·56%	<0·01%	1	1	CR, MRD Neg	1	0	46

M=male. F=female. C=chemotherapy. R=radiation therapy. I=immunotherapy. T=allogeneic haemopoietic stem-cell transplant. CAR=CD19 chimeric antigen receptor. CRS=cytokine release syndrome. CR=complete response. MRD Neg=no minimal residual disease detected. CRi=CR with incomplete count recovery. SD=stable disease. PD=progressive disease. HSCT=haemopoietic stem-cell transplant. *Diffuse large B-cell lymphoma. †Actual dose received was $3·6 \times 10^6$ CAR T cells per kg. ‡Tocilizumab. §Corticosteroid.

Table 1: **Patient demographic characteristics, response, and toxicity**

Source: Lee D et al. *Lancet* 2014

We view these results favorably, as proof of concept in the NCI's CAR T-cell technology in the treatment of relapsed/refractory ALL patients. Although these results were lower than the 88% CR rate reported by MSKCC group, the MSKCC group included 2 patients with MRD negative disease rendered by chemotherapy, potentially confounding the role of CAR T-cell therapy. Based on the results of this trial, we believe Kite will file an IND to initiate a relapsed/refractory ALL trial of its own using KTE-C19, possibly in 2015.

COMPETITION MANAGEABLE

NOVARTIS TARGETS ALL AND CLL

Novartis has an exclusive global agreement with the University Of Pennsylvania School Of Medicine. Under the terms of the agreement, UPenn has granted Novartis an exclusive worldwide license to CARs developed through the collaboration for all indications and CTL019, UPenn's version of CAR T-cell therapy. In addition, Novartis will provide an up-front payment, research funding, funding for the establishment of the CACT and milestone payments for the achievement of certain clinical, regulatory and commercial milestones and royalty payments. To date, UPenn has only published data on adult and pediatric ALL and CLL.

Figure 20: Current clinical trials for UPenn with CAR T-cell therapy

Cancers	Title	Trial	Inclusion	Study Arm	Primary Endpoints	Secondary Endpoints
B-ALL	Study of Redirected Autologous T Cells Engineered to Contain Anti-CD19 Attached to TCR and 4-1BB Signaling Domains in Patients With Chemotherapy Resistant or Refractory Acute Lymphoblastic Leukemia	Phase 2 NCT02030847 Start Jan 2014 Est time of completion - 1/2015 Est enrollment - 24 pts	Relapsed or refractory B-cell ALL a. 1st or greater BM relapse b. Any marrow relapse after allogeneic HSCT and 100 days from transplant OR c. For patients with refractory disease: d. Patients with Ph+ ALL are eligible if they have failed tyrosine kinase inhibitor therapy	Single Arm	Number of adverse events	
NHL	Phase IIa Study of Redirected Autologous T Cells Engineered to Contain Anti-CD19 Attached to TCRz and 4-Signaling Domains in Patients With Chemotherapy Relapsed or Refractory CD19+ Lymphomas	Phase 2 NCT02030834 Start Jan 2014 Est completion - July 2015 Est enroll 55 pts	CD19 B-cell lymphomas with no available curative tx who have limied prognosis (<2 yrs survival) Enroll 30 pts, will ensure at least 8 pts each with DLBCL, MCL, and FL	Single arm	Efficacy	
ALL	Allo CART-19 Protocol	Phase 1 NCT01551043 Start Sept 2012 Est completion - Sept 2013 Not enrolling anymore	CD19+ ALL relapsed after allogeneic SCT	Single arm	Safety	
MM	CART-19 for multiple myeloma	Phase 1 NCT02135406 Start May 2014 Est completion - May 2016 est enroll 15 pts	Patients who have undergone a prior ASCT for MM and progressed within 1 year Can have 2 prior ASCTs as part of a planned tandem ASCT consolidation	Single arm	Safety, tolerability, efficacy	
CLL	CD19 Redirected Autologous T Cells	Phase 2 NCT01747486 Start Dec 2012 Est completion - Dec 2015 Est enroll 32 pts	CLL/SLL who have received at least 2 prior chemotherapy regimens	2 arms: 1. 1x10^8 2. 1x10^7	Safety and efficacy	
All B-cell leukemia /lymphoma Pediatric	Phase I/IIA Study of CART19 Cells for Patients With Chemotherapy Resistant or Refractory CD19+ Leukemia and Lymphoma **(Pedi CART-19)**	Phase 1 NCT01626495 Start Aug 2011 Est completion - Aug 2016 Est enroll 20 pts	CD19 B-cell malignancies 1 - 24 years old	Single arm	Safety and efficacy	1. Ability of 2 different CART cells to expand and persist 2. Impact of CART infusion on cancer

Source: Clinicaltrials.gov

Pediatric and adult ALL show promising results, but not without cost

UPenn recently reported an astounding 90% complete response rate in ALL, an impressive result, but some safety concerns appeared. Sustained remission was achieved with a 6-month event-free survival rate of 76% (95% CI, 51 to 88) and an overall survival rate of 78% (95% CI, 65 to 95%). The pilot study treated 30 patients (25 children and 5 adults) with relapsed, refractory ALL, with historical response rates of less than 30%. 80% of patients had detectable disease prior to T-cell infusion, though the paper does not comment on the extent of disease burden at baseline.

Figure 21: Response rate in relapsed/refractory ALL

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Pediatric Cohort (N=25)	Adult Cohort (N=5)	Total (N=30)
Sex — no. (%)			
Female	11 (44)	1 (20)	12 (40)
Male	14 (56)	4 (80)	18 (60)
Age at infusion — yr			
Median	11	47	14
Range	5–22	26–60	5–60
Allogeneic transplantation — no. (%)	18 (72)	0	18 (60)
Primary refractory disease — no. (%)	0	3 (60)	3 (10)
Relapse — no. (%)			
1	3 (12)	2 (40)	5 (17)
≥2	22 (88)		22 (73)
Baseline burden of acute lymphoblastic leukemia — no. (%)			
Presence of detectable disease†	20 (80)	4 (80)	24 (80)
Morphologic remission‡		1 (20)	1 (3)
Absence of minimal residual disease	5 (20)		5 (17)
High-risk cytogenetic factors — no.			
BCR–ABL1	2		
IKZF1 deletion	2		
iAMP21	1		
MLL translocation	1		
Hypodiploidy	2		
CNS status — no.§			
CNS-1	23		
CNS-2	2		

Source: Grupp S et al. *55th ASH Annual Meeting* 2013; abstract 67

Despite the positive responses seen, the delayed CRS experienced by patients remains a concern. This phenomenon is believed to be the result of T-cells killing malignant cells, causing a cytokine storm that involves high fevers, bone aches, and possibly ICU admission for hemodynamic insufficiency. All patients (100%) developed some degree of toxicity, mainly cytokine release syndrome (CRS). Treatment for CRS was required for hemodynamic or respiratory instability in 8/30 patients and was reversed in all cases with the usage of tocilizumab (9 pts), an IL-6 inhibitor and steroids. Persistence of CTL019 cells with ongoing response was detected for as long as 2 years after infusion, demonstrating the robust in vivo expansion of CTL019 in patients and prolonged duration of response.

Long-term persistence and durable response in relapsed/refractory CLL

UPenn has also noted durable and persistent responses in CLL, with an ORR of 57%, including n=4 patients with CR (29%) and n=4 patients with PR (29%) at 9.4 months. For patients with CR, duration lasted between 11 – 35 months, with persistence of T-cells found by flow cytometry in all 6 responding patients. Data was presented by UPenn in 14 relapsed/refractory CLL patients (progressed at least after 2 previous treatments) at ASH 2013. All patients had received a median of 4 prior therapies (1-10), with 6 patients having the worse prognostic factor of p53 mutation. All patients had active disease at time of therapy of CTL019, with lymphopleting chemotherapy as either FC, PC, or bendamustine. A total dose of 5x10^8 – 2 x 10^9 total cells were given over 3 days (10% on day 1, 30% on day 2, and 60% on day 3).

However, CRS was noticed again in all responding patients concurrent with T-cell expansion, manifested by myalgia, hypotension, hypoxia, and fever. Intervention was needed in 5 patients with tocilizumab and steroids.

Figure 22: Response rate in relapsed/refractory CLL

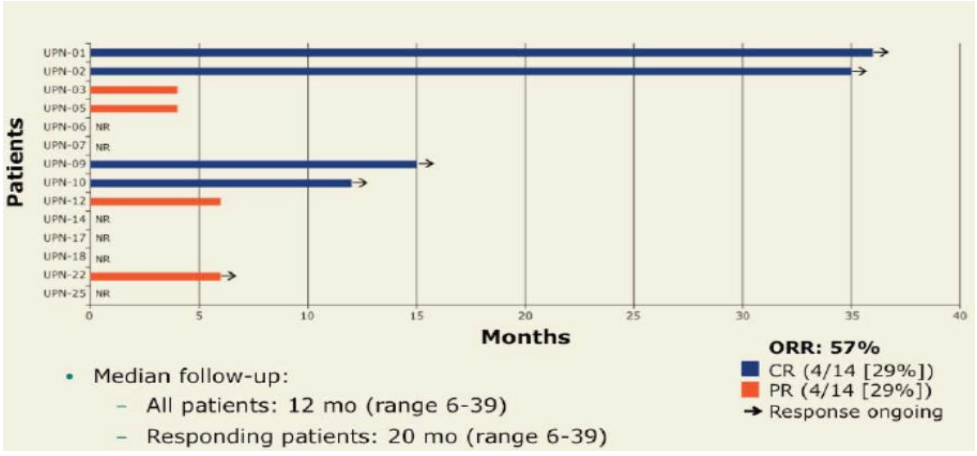
Best response	n = 14
Overall response rate Complete response (CR)* Partial response (PR)	8 (57%) 4 (29%) 4 (29%)
No response	6 (43%)

* 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

Source: Porter D et al. *55th ASH Annual Meeting* 2013; abstract 4162

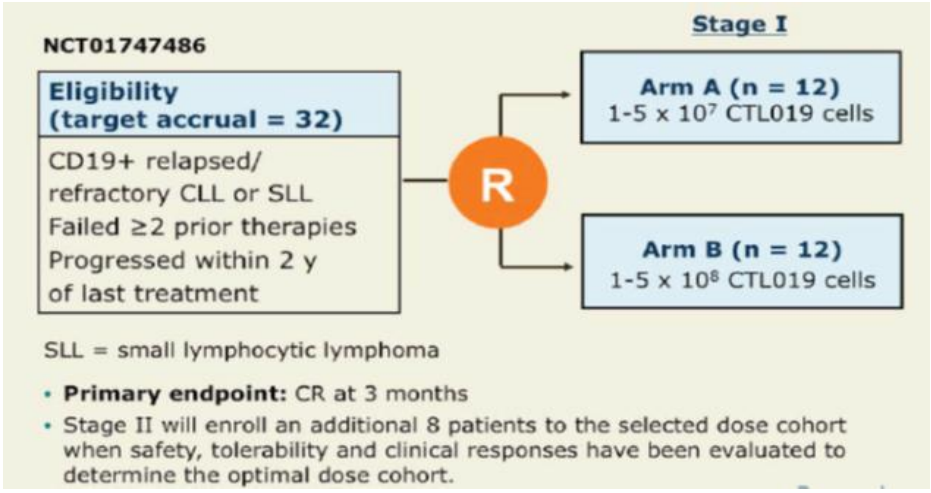
Figure 23: Duration of response in CLL



Source: Porter D et al. *55th ASH Annual Meeting* 2013; abstract 4162

Due to these long-term data, another current ongoing phase 2 trial is being conducted in CD19 relapsed/refractory CLL patients who failed ≥ 2 prior therapies, with study design presented below. Unlike the previous trial, this is a randomized clinical trial to evaluate two different dosages of CAR T-cell and its value on efficacy and safety.

Figure 24: Randomized Ph 2 Dose Optimization Trial of CTL019 in relapsed/refractory CLL



Source: Porter D et al. *55th ASH Annual Meeting* 2013; abstract 873

Currently, out of 18 patients evaluated, 3 (17%) achieved CR, 4 (22%) achieved PR for a total ORR of 7 (39%) with a median follow-up of 3.3 months. No difference in toxicity or response was seen between the two groups (Group B used similar dose compared to previous CLL trial), giving rise to the hypothesis that lower doses can be administered since in vivo expansion occurred the same in both arms. Additionally, efficacy was considerably lower compared to the first CLL trial, highlighting the heterogeneous tumor microenvironment in CLL patients. Again, similar CRS side effects were observed in responding patients, with 2 patients requiring hemodynamic and respiratory instability.

Kite does not have reports in CLL patients, but does allow enrollment of relapsed/refractory CLL patients in their ongoing clinical trial. Though it remains difficult to compare between the disease states, the toxicities between the two companies appear heightened with UPenn's construct, displaying more hemodynamic instability.

JUNO SUCCESS IN ALL

Juno has its own chimeric antigen receptor technology in partnership with Memorial Sloan-Kettering Cancer center, Fred Hutchinson Cancer Research Center and Seattle Children's Research institute. It is also in collaboration with MabVax Therapeutics Holdings, a clinical stage oncology drug development company that will supply unique targeting sequences from the fully-human antibodies to MSKCC researchers in hopes of producing anti-cancer agents targeting solid tumors. MabVax currently has a pipeline of eleven separate fully human antibodies targeting various solid tumor cancers.

Figure 25: Current clinical trials for MSKCC and Fred Hutchinson with CAR T-cell therapy

Cancers	Title	Trial	Inclusion	Study Arm	Primary Endpoints	Secondary Endpoints
All B-cell leukemia /lymphoma	Laboratory Treated T Cells in Treating Patients With Relapsed or Refractory Chronic Lymphocytic Leukemia, Non-Hodgkin Lymphoma, or Acute Lymphoblastic Leukemia	Phase 1/2 NCT01865617 Start May 2013 Est completion - April 2029 After completion, patients followed for 15 yrs	All patients with CD19 disease (CLL, NHL, MCL, NHL, DLBCL, ALL)	Single arm: Treatment with CART cells	Safety and feasibility OS PFS	1. Duration of Tcells 2. To see if disease goes to BM and function in vivo 3. To see if CART depletes CD19 4. Antiumor activity 5. TLS
ALL	Precursor B Cell Acute Lymphoblastic Leukemia (B-ALL) Treated With Autologous T Cells Genetically Targeted to the B Cell Specific Antigen CD19	Phase 1 NCT01044069 Start Jan 2010 Est completion - Jan 2015 Est enrollment - 40 pts	B-ALL patients (refractory, relapsed, MRD, or in first CR	Single arm	Safety and efficacy	Anti-leukemic effect
CLL indolent B-cell lymphoma	Treatment of Relapsed or Chemotherapy Refractory Chronic Lymphocytic Leukemia or Indolent B Cell Lymphoma Using Autologous T Cells Genetically Targeted to the B Cell Specific Antigen CD19	Phase 1/2 NCT00466531 Start March 2007 Est completion - Dec 2014 Est enrollment - 30 pts	CD19 B-cell leukemia or lymphoma	Single arm	Phase 1: safety Phase 2a: to see engraftment of 41bb vs. 28z	Anti-leukemic effect

Source: Clinicaltrials.gov

Focus on ALL, safety critical issue

MSKCC reported strong data in relapsed/refractory ALL patients, making this disease the primary focus for Juno. In its phase 1 clinical trial for adults with relapsed/refractory B-ALL (currently treated 16 patients), patients are infused with 3 x 10^6 cells/kg following conditioning chemotherapy of cyclophosphamide. CAR T-cell products were successfully generated in 15 of 16 patients. Data showed an impressive 88% overall complete response rate in a disease where salvage conventional chemotherapy only produces 20-30% total response rates, far exceeding expectations. Furthermore, in patients wherein the malignant tumor clone could be monitored in bone marrow by deep sequencing, researchers found rapid elimination of the malignant clones after infusion in 86% of the responders. Nearly all patients had peak CAR T-cells within 1-2 weeks after infusion,

which remained elevated for 2-3 months. Due to this therapy, physicians at MSKCC successfully transitioned 7 patients (44%) to allo-SCT, which is considered the main goal for CAR T-cell therapy in ALL. This is especially meaningful since only ~5% of patients transition to allo-SCT from relapsed/refractory ALL, making this an effective "bridge" to allo-SCT. Because of the deep complete responses achieved by this technology, investigators hypothesize that transplants performed under these optimal conditions will markedly, if not completely, reduce the historical 30% disease relapse rate of B-ALL patients after allo-SCT.

Figure 26: Response rate of CAR T-cell therapy in ALL - MSKCC

Characteristics	No. of patients (*N* = 16)	%
Overall complete response to salvage chemotherapy*	7	44
Overall complete response to 19-28z CAR T cells	14†	88
In patients with morphologic residual leukemia (*n* = 9)	7	78
Complete remission (CR)	10	63
Complete remission with incomplete count recovery (CRi)	4	25
Molecular complete remission (CRm)‡	12†	75
Median time to CR/CRi (days)	24.5	
Post-CAR T allo-SCT (*n* = 10 eligible patients)§	7	70

*Overall complete response = CR + CRi (determined without regard to CRm status). †Includes two patients who were in CRm before CAR T cell infusion. ‡CRm or MRD⁻ as determined by flow cytometry and/or deep sequencing for the index *IgH* clonotype and/or qPCR for the *bcr-abl* transcript. §Three patients had medical contraindication to allo-SCT, two patients in CR have declined potential allo-SCT, and one is being evaluated for an allo-SCT.

Source: Davila M et al. *Sci Transl Med* 2014

Compared to the data from UPenn where reports of ALL and several CLL patients had persistent T-cells for several months to more than a year, the duration of CAR T-cells in ALL patients is only 3 months. It remains possible that the MSKCC construct of 19-28z CAR T-cell expansion and subsequent contractions are CD19 antigen–dependent, resulting in T-cell clearance upon elimination of normal and malignant and B-cells, as seen in a normal T-cell immune response to antigen. Accordingly, the persistence of CD19-targeted CARs incorporating a 4-1BB moiety rather than CD28 as used by UPenn may be due, at least in part, to antigen-independent signaling through the 4-1BB CAR.

Safety issues included Cytokine Release Syndrome, but managed

The administration of CAR T-cells induced serious clinical cytokine release syndrome, including fevers, hypotension, hypoxia, and neurologic changes. Unlike the toxicities associated with conventional salvage chemotherapy, those associated with infused CAR T-cells are related to large-scale, synchronous T-cell activation upon targeting of CD19 leukemia cells. Interestingly, an in-depth analysis identified a correlation between pretreatment tumor burden and high cytokine levels. Similar to other institutions, clinically alarming neurologic changes associated with cytokine release syndrome was noted. Recently, deaths of two patients with 2 weeks of CAR T-cell administration sparked controversy and eventually led to a temporary halt of clinical trials by MSKCC. One patient had a history of cardiac failure and the other developed persistent seizures following her second infusion of CAR T-cells. It should be noted that these two patients were sicker than the average patients treated with this therapy, including the second patient having already received CAR T-cells initially, relapsed and treated again with CAR T-cells.

CLL supported by phase 1 data

MSKCC also studied the CAR T-cell technology in a phase 1 clinical trial with CLL patients with residual disease following first-line chemotherapy, producing an ORR of ~57%, which is comparable to UPenn. In this study, patients with CLL who have achieved either PR or CR to first-line therapy were enrolled. The trial enrolled 7 patients, with 4 patients still having palpable lymphadenopathy prior to T-cell infusion. 1 patient achieved CR (14%); 2 pts achieved CR in the bone marrow but had progressive disease in lymph node only (29%); 3 pts achieved PR (43%); and 1 pt had progressive disease (14%). Mild and self-limiting CRS was observed in 3 patients, with a positive correlation between the development of CRS and the CAR T-cell persistence. Though only a limited number of patients treated, conclusions from this trial infer that the treatment with CD19 CAR T-cells is more effective in eradicating disease in the bone marrow than in the lymph nodes.

Similar to UPenn's data, the limited clinical efficacy of CAR T-cells was again seen when compared to results in ALL. Potential explanations for the limited clinical efficacy of CAR T-cells in patients with CLL compared to B-ALL is the limited persistence of CAR T-cells in patients with CLL, the immuno-inhibitory tumor microenvironment of CLL, the mostly bone marrow-based nature of B-ALL compared to the lymph-node based disease in CLL, and the lower tumor burden at treatment in patients with B-ALL.

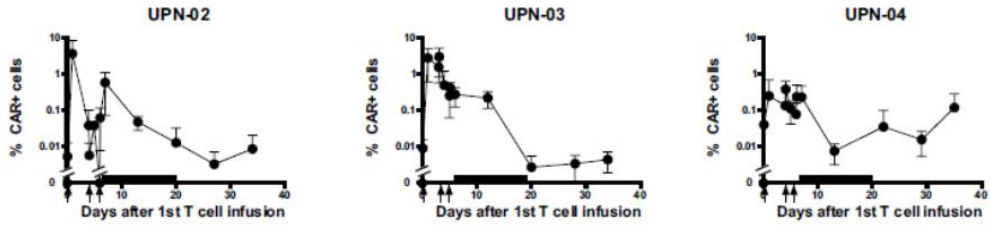
Next generation CAR T-cells for lymphoma from Fred Hutchinson Cancer Center and Seattle Washington's Children Hospital

The trials at these centers focus on the treatment of relapsed NHL after failure of one line of chemotherapy with CAR T-cells targeting CD20 instead of CD19 antigen, a well-established immunotherapy target commonly found on the surface of nearly all B-cell NHLs. Additionally, to improve the efficacy from "second generation" CARs where only one co-stimulatory endodomain is used (CD28, 4-1BB, OX40), the group at Fred Hutchinson linked the endodomains of CD28 and 4-1BB together in hopes that these "third generation" CARs may elicit a more potent immunogenic response. Additionally, instead of using a retrovirus or lentivirus, gene transfer was done by electroporation. This process of gene transfer is highly inefficient and necessitates antibiotic selection of transfectants during expansion. The trial is still in its early phases, but data on four enrolled patients (3MCL, 1 FL) were recently published in patients with relapsed indolent B-cell and mantle cell lymphoma. Similar to previous trials presented, patients received induction lymphodepleting chemotherapy 2 days before cell infusion. However, to increase in-vivo T-cell expansion, 14 days of SQ IL-2 injections were given.

Results show that treatment was well tolerated despite some manageable infusion reactions. However, given the low sample size, conclusions from this trial is limited. It is also possible that a third-generation CAR could engender significant toxicity if expressed at higher levels. The clinical results of this therapy were promising, with 2 patients without evaluable disease remained progression free for 12-24 months and a third patient had an objective partial remission, but relapsed 1 year later. This is encouraging given that the median time to progression for relapsed MCL in most clinical trials is approximately 6 months. Limitations lie in the feasibility of the construct. Electroporation of naked plasmid DNA results in prolonged and intensive use of many resources (personnel, cGMP facilities…etc.) and is not practical for scaling up to treat

larger number of patients. Furthermore, the method probably impairs T-cell functionality and potential for in vivo expansion, as seen with the low levels of CAR expression that were below detectable range by flow cytometry.

Figure 27: Engraftment and persistence of CAR T-cell by quantitative real-time PCR



Source: Till B et al. *Blood* 2012

CELGENE/BLUEBIRD, PFIZER/CELLECTIS, GLAXO/ADAPTIMMUNE, TAKARA, BELLICUM ALSO IN RACE

Additionally, four other companies are currently in the CAR T-cell race, though we believe the competition is manageable.

Bluebird/Celgene

In a global collaboration with Celgene Corporation and working Baylor College of Medicine, Bluebird Bio is in development of its own CAR T-cell therapy for various hematologic malignancies, currently in preclinical trials. Under the collaboration agreement with Celgene, Bluebird may develop product candidates covered by the IP rights of Baylor in this field, and intellectual property rights would be in-licensed by Celgene pursuant to its collaboration agreement with Baylor.

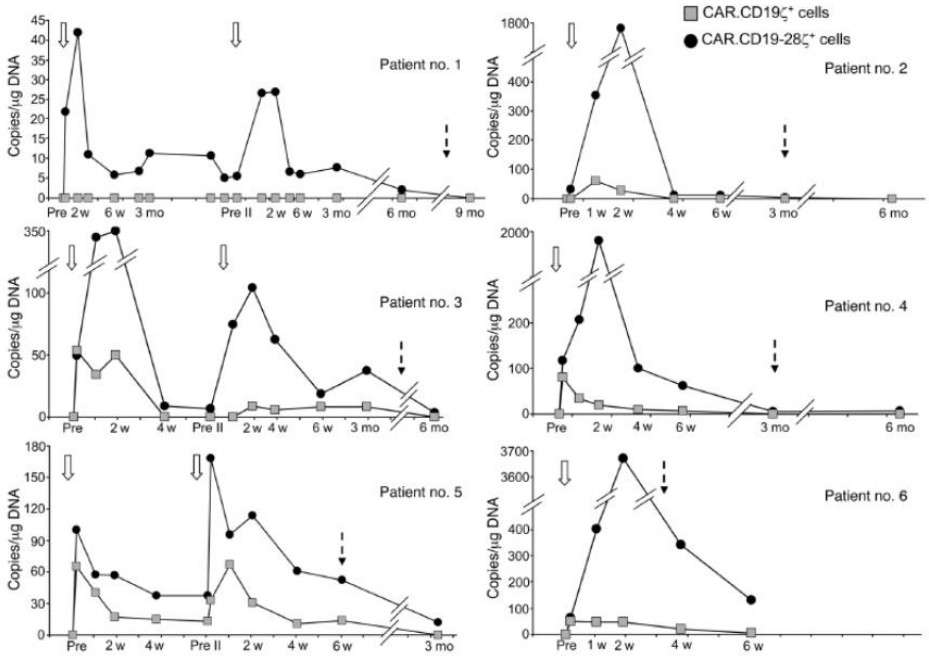
Figure 28: Current clinical trials for Bluebird/Celgene with CAR T-cell therapy

NHL ALL B-CLL	CD19 Chimeric Receptor Expressing T Lymphocytes In B-Cell Non Hodgkin's Lymphoma, ALL & CLL (CRETI-NH)	Phase 1 NCT00586391 Start Feb 2009 Est completion - Feb 2018 Est enrollment - 54 pts	Recurrent low grade of intermediate grade B-cell lymphoma or leukemia (ALL or CLL)	Single arm dose level elevation	Safety and efficacy	1. Survival of CART cells 2. Tumor response
NHL CLL	Activated T-Cells Expressing 2nd or 3rd Generation CD19-Specific CAR, Advanced B-Cell NHL and CLL (SAGAN) CD19-28 or CD19-28-137	Phase 1 NCT01853631 Start Feb 2014 Est completion - Feb 2017 Est enrollment - 14 pts	1. Recurrent aggressive or indolent B-cell lymphoma or CLL 2. Newly diagnosed relapsed/refractory B-cell lymphoma	Single arm	Safety: # of pts with DLT	1. Survival of CART 2. Tumor response 3. % of circulating CART after additional doses 4. Function of CD19 CAR-ATLs
ALL CLL NHL	Activated T Lymphocytes Expressing CARs, Relapsed CD19+ Malignancies Post-Allo HSCT (CARPASCIO)	Phase 1 NCT02050347 Start April 2014 Est completion - March 2018 Est enrollment - 56 pts	CD19 B-ALL or CD19 B-CLL or NHL	2 dose escalation scheme for ALL and CLL/NHL	Safety: DLT	Tumor response and frequency of T-cell products

Source: Clinicaltrials.gov

Baylor College of Medicine was the first institution to compare "first generation" CAR T-cells against "second generation" CAR T-cells in patients with B-cell lymphomas to answer the question of whether dual signaling domains can increase persistence and expansion of the T-cells. With a total of 6 NHL patients, the investigations simultaneously infused 2 autologous T-cell products, each containing cells that expressed an identical CAR exodomain specific for the CD19 antigen. However, one CAR was coupled with the ζ-endodomain alone, while the second product CAR was coupled to both the CD28 and ζ-endodomain. Results show that the CAR CD19-28 T-cells reached a nadir by 4 to 6 weeks after infusion. CAR CD19-28 signals were significantly higher than single signaling domain signals at every time point tested over the first 4 weeks after infusion. This proof-of-concept study built the foundations for their CAR T-cell platform and demonstrated the superiority of CARs with dual signal domains. Additionally, it confirms a method of comparing CAR-modified T-cells within individual patients, thereby avoiding patient-to-patient variability and accelerating the development of optimal T-cell immunotherapies.

Figure 29: in vivo expansion and persistence of infused CAR T-cell



Source: Savoldo B et al. *J Clin Invest* 2011

Cellectis/Pfizer

On June 18, 2014, Pfizer announced a global strategic cancer immunotherapy collaboration with Cellectis for CAR T-cells. Under the terms of the agreement, Pfizer has exclusive rights to pursue development and commercialization of CAR-T therapies in the field of oncology with a total of fifteen targets selected by Pfizer and twelve targets selected by Cellectis.

Glaxo/Adaptimmune

GSK also threw its hat in the ring by entering into collaboration and licensing agreement with Adaptimmune Limited, a biotechnology company developing TCR engineered T-cells to treat cancer. Adaptimmune has created TCRs which are deployed to target the cancer testis antigen, NY-ESO-1, and other targets for multiple myeloma, melanoma, sarcoma and ovarian cancer. Under the agreement, Adaptimmune will co-develop its NY-ESO-1 clinical program with GSK having an option and exercise on the program through clinical proof of concept, expected in 2016.

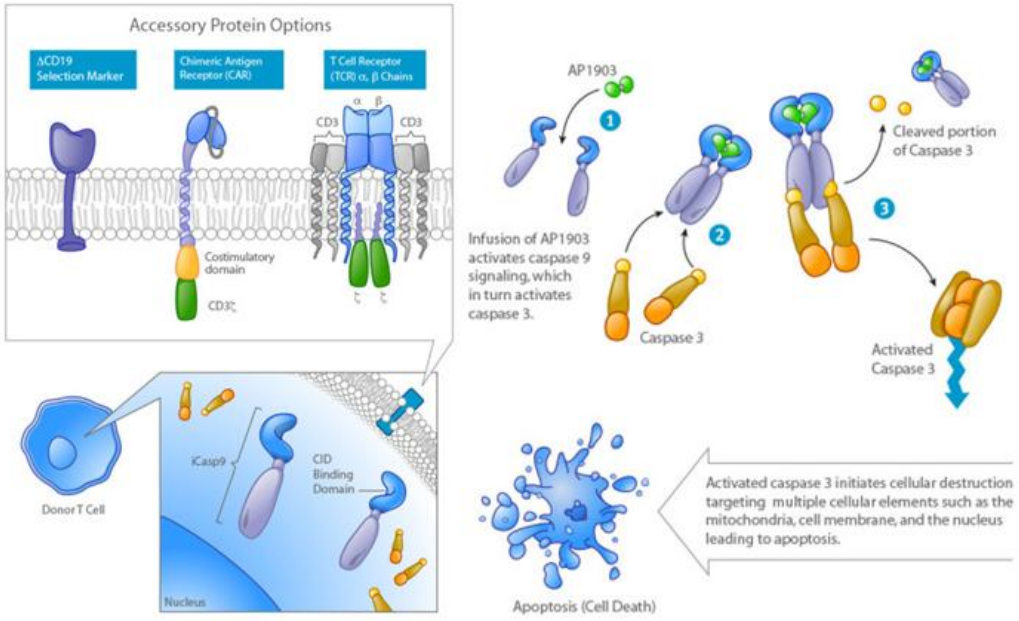
Takara Bio

Takara Bio has recently entered the immunotherapy space when it recently announced its application to conduct clinical research in Japan using C19 antigen specific CAR T cells for NHL. Additionally, the company has also filed applications for Phase 1 clinical trials on MAGE-A4 antigen specific TCR to start soon in Japan.

Bellicum

The cytokine release syndrome that occurs with CAR T-cell therapies remains a significant limitation to CAR T-cell therapy. The magnitude of immune activation typically required to mediate clinical benefit exceeds levels of immune activation that occurs in more natural settings. As immune-based therapies become more potent, so may the side effects. After the deaths from MSKCC, clinicians have shifted the focus primarily to safety. Bellicum, with its unique iCasp9 technology, is currently in the frontier of producing a "control switch" to regulate the level of T-cells activation in vivo, potentially giving physicians authority over immune activity inside the body and mitigating the toxic CRS to patients. This is potentially useful as a stopping mechanism in case patients undergo severe cytokine storm following immunologic therapy with CAR T-cells. The CID technology can potentially be used in combination with current CAR T-cell therapies by acting as a "suicide gene" in their CaspaCIDe platform. In the presence of their activating drug, AP1903, rapid death would be triggered in the cells containing the CaspaCIDe safety switch. CID proteins are created by modifying a pre-existing, naturally occurring signal protein to include a region designed to bind only to AP1903. Through a viral vector, the switch is re-introduced into the patient. When AP1903 is administered, the modified proteins bind to each end of the drug molecule, forcing the CID proteins to dimerize. Dimerization activates caspase 9 and 3 signaling. The activated caspase 3 initiates cellular destruction, thus turning off the signal cascade. We feel this may represent the next generation CAR T-cells where the potency can be maximized while having the security of a kill switch in case of immune overstimulation.

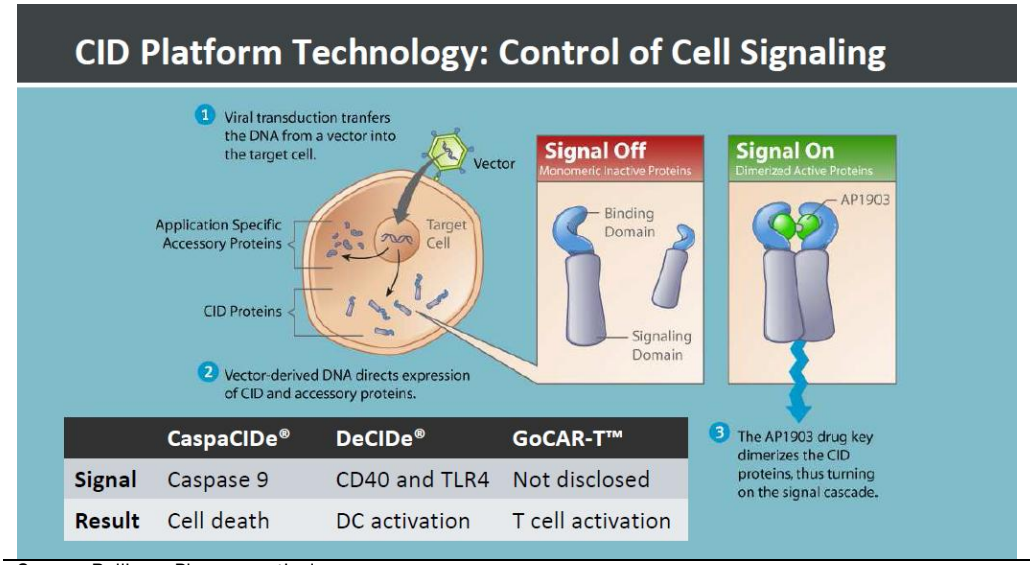
Figure 30: Mechanism of action of CID technology



Source: Bellicum Website

On the other spectrum, the company is using its Chemical Induction of Dimerization (CID) technology for T-cell activation instead of T-cell killing. The CID technology enables modulating T-cells engineered with specialized cell signaling switches that can only be controlled by a specifically designed activator drug. The drug, AP1903, is a fully synthetic small molecule compound used exclusively to control cell therapies that have been modified with their GoCAR-T technology. The figure below shows activation of T-cells only though the infusion of AP1903, which dimerizes the active CID proteins. Only through its presence can the T-cells remain in an active state, giving physicians the ability to slowly titrate the immune response to an appropriate level instead of the violent activation seen CAR – antigen engagement.

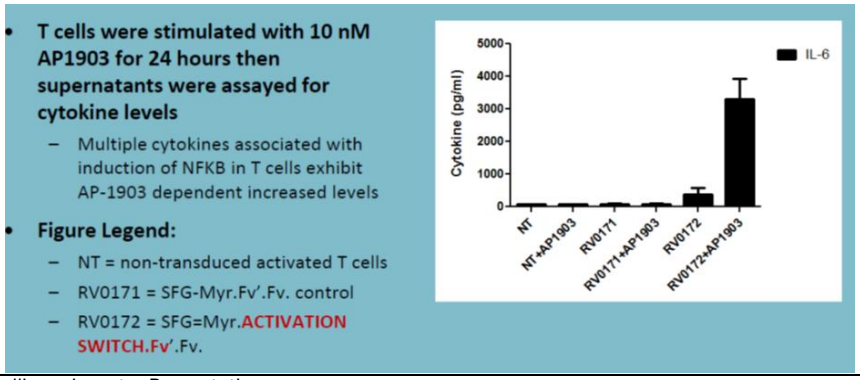
Figure 31: CID Platform for T-cell activation



Source: Bellicum Pharmaceuticals

The graph below shows the modified GoCAR T-cells stimulated only in the presence of AP1903. Therefore, clinicians can slowly titrate doses of AP1903 to efficacy while maintaining the therapeutic window.

Figure 32: Cytokine stimulation with AP1901 in vitro



Source: Bellicum Investor Presentation

Other cancer immunotherapy companies

Riding the momentum from recent advances in T-cell therapy, a number of additional companies have entered the field of cancer immunotherapy. These companies, including Immune Design, Scancell, CellDex, Aduro, and Unum, are targeting similar antigens as the companies previously described, including NY-ESO-1 and EGFRvIII, but with different methodologies. For example, Immune Design's platform is designed to activate and expand the immune system's natural ability to create tumor-specific cytotoxic T-cells (CTLs) in vivo, hoping to kill tumor cells bearing that same specific tumor antigen. Celldex, on the other hand, is studying active immunotherapy combined with vaccines against EGFRvIII-expressing tumors. We await further results from these companies and the role they will play in the next generation of cancer treatment.

Figure 33: Current cancer immunotherapy companies

Company	Technology	Vector	Target	Indication	Partners
KITE	CART TCR	Retrovirus Retrovirus	CD19, EGFRvIII NY-ESO-1; SSX2; MAGE	DLBCL, hematologic malignancies, GBM Solid Tumors	(NIH)
Novartis	CART	Lentivirus	CD19	Hematologic malignancies	(UPenn)
Juno	CART	Retrovirus	CD19	Hematologic malignancies	(MSKCC/Fred Hutch)
Bluebird	CART	Retrovirus	CD19	Hematologic malignancies	Celgene
Cellectis	CART TCR	- -	CD19 EGFRvIII; others undisclosed	Hematologic malignancies Solid Tumors	Pfizer
Takara	CART TCR	Retrovirus Retrovirus	CD19 MAGE-A4; NY-ESO-1	Hematologic malignancies Solid Tumors	
Adaptimmune	TCR	Lentivirus	NY-ESO-1; others undisclosed	Solid Tumors	GSK
Unum	Antibody coupled TCR	-	-	-	-
Bellicum	GoCART Cancer Vaccine (DeCIDE)	- -	CD19, others undisclosed -	Hematologic malignancies / Solid Tumors Hematologic malignancies / Solid Tumors	
Immune Design	Cytotoxic T cells (CTL)	-	NY-ESO-1	Solid Tumors; Merkel Cell Carcinoma	Sanofi/MedImmune
Aduro	Cancer Vaccine/listeria immunotherapy	-	Various tumor antigen cell line	Pancreatic, mesothelioma, GBM, Ovarian, NSCLC, Prostate	Janssen Biotech
Scancell	Cancer Vaccine / immunotherapy	-	NY-ESO-1	Melanoma, various solid tumors	-
CellDex	Cancer Vaccine / immunotherapy	-	EGFRvIII; NY-ESO-1; CD27	GBM, TNBC, Hematologic and Solid tumors	-

Source: Canaccord Genuity research

CART BACKGROUND: NOVEL CELLULAR THERAPIES TARGETED TO THE CD19 ANTIGEN

INTRODUCTION: IMMUNOTHERAPY OVERVIEW

The success of gene therapy over the years has demonstrated significant potential as a targeted cancer therapy by stimulating the immune system to evoke natural responses against malignant cells. A coalescence of preclinical, and now clinical, studies are available to support the premise of gene transfer combined with adaptive cellular therapy to overcome the fundamental limitations of own body's intolerance to the disease. There are many mechanisms that prevent the immune system from eliminating cancer cells. One major reason is the low affinity of T-cell receptors (TCR) for self-antigens compared with foreign antigens. Therefore, adaptive transfer using viral engineered TCRs and CARs remain a promising approach to overcome the low potency of the body's own TCR. Within this section, we will outline the progression of immune therapy, from the lackluster results of cancer vaccines to the current state of the popular CAR T-cell therapy.

CANCER VACCINE – LITTLE SUCCESS TO DATE

Identification of immunogenic tumor-antigens initially attracted many clinicians into the field of translational research, leading to trials involving cancer vaccines. Recently, a panel of preparations for cancer vaccine has been tested for their ability to elicit tumor-specific immune responses and induce anti-tumor effects in vivo. However, only sipuleucel-T (Provenge), a cell-based vaccine, has been clinically approved for the treatment of metastatic hormone-refractory prostate cancer, with only a modest survival benefit. The poor transition from bench top to the clinic in cancer vaccine is reflected on the limitations of cancer vaccines itself: 1) poor recognition to the tumor antigen, 2) vaccines themselves do not induce potent systemic effects, and 3) low expression of antigens in tumor cells themselves. The figure below shows current clinical trials with various cancer antigen targets. Despite the discovery of these targets, lack of efficacy restricts the potential of cancer vaccines. For example, the recent MAGRIT trial of 2270 NSCLC targeting the MAGE-A3 antigen failed to show disease-free survival compared to placebo, reflecting the need for more potent therapies against these cancer targets.

Figure 34: Recent clinical trials of cancer vaccines with purified tumor-associated antigen

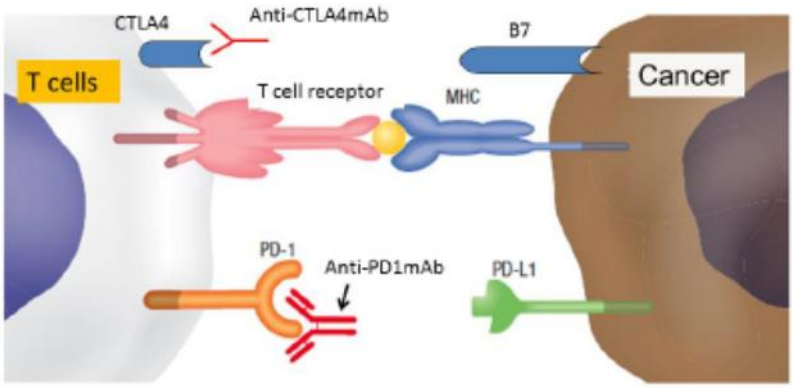
Indication	Clinical Trial	Antigen
Hematological malignancy (AML, CML...etc)	Phase I	NY-ESO-1
Hematological malignancy (AML, CML...etc)	Phase I/II	MAGE-A10; WT1
Breast Cancer	Phase II	HER2
Cervical cancer	Phase I	E7
Melanoma	Phase I	NY-ESO-1; BCAR3; MAGE-A3.A1
Mesothelioma	Phase II	WT1
NSLCL	Phase I/II	MUC1; TERT

Source: Kono K et al. *JSRM* 2014

IMMUNE CHECKPOINTS

The lack of robust efficacy from the vaccine trials led to an important discovery regarding the binding of T-cells to the antigens. The interaction between T-cells and the tumor is dependent on the quality and grade of their interaction, regulated through both activating and inactivating signals (aka, immune checkpoints). Under normal conditions, immune checkpoints play a crucial role in preventing autoimmunity and protecting tissue damage from one's own immune system. However, tumor pathogenesis can cause an up-regulation of these signals, leading to a cancer evasion mechanism. Currently, two immune checkpoint receptors have been recognized and actively studied in the clinic: cytotoxic T-lymphocyte-associated antigen 4 (CTLA4) and programmed cell death protein 1 (PD1). CTLA4 inhibits the activity of the T-cell co-stimulatory receptor CD28, where CD28 causes inhibition of T-cells. Marked PD1 expression has been reported in various malignancies, mainly expressed after exposure to inflammatory cytokines.

Figure 35: Immune checkpoint blockade with monoclonal antibodies



Source: Kono K et al. *JSRM* 2014

In 2010, reports from NEJM showed nivolumab (PD1 inhibitor) plus ipilumumab (CTLA inhibitor) survival benefit in advanced melanoma. Further studies with PD1 inhibitors show further tumor shrinkage in about half or more in 31% of patients with melanoma, 29% with kidney cancer, and 17% with lung cancer (Hamid O. et al. NEJM 2013). Further use of this technology in blocking crucial immune checkpoint pathways, like PD1 and CTLA4, is expected going forward.

CHIMERIC ANTIGEN RECEPTOR T-CELLS

Chimeric Antigen Receptor T (CAR T) cells are currently focused on B-cell malignancies, and are a novel way to target the body's own immune system to blood borne cancers. CAR T-cells involve developing genetically modified T-cells against the common CD19 antigen found in most hematologic cancers. Once bound to the antigen, the T-cell biopharmaceutical product should have the ability to lyse the tumor cells expressing the particular marker. The ideal case for effective treatment must have the following properties:

1. It is immunogenic;

2. It is completely tumor-specific with no significant expression on normal tissues;

3. It is highly expressed on the surface of all tumor cells;

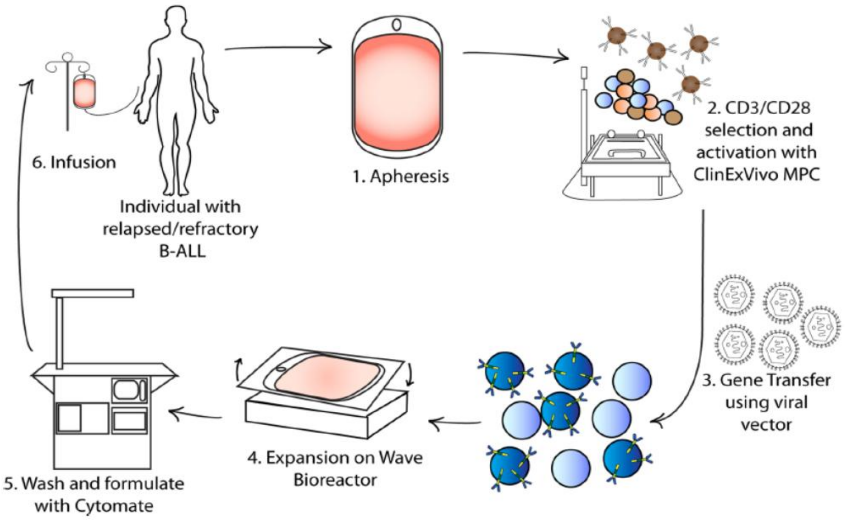
4. It is essential for survival or proliferation of the tumor cell;

5. It has multiple epitopes.

CLINICAL CONCEPT OF CAR T-CELL THERAPY

The technology available to KITE and other institutions relies on the modification of patient's own T-cells to recognize and eradicate CD19 antigen presenting malignancies. In the figure below (Davila M. et al, Int J Hematol. 2014), patients are leukapheresed where T-cells are positively selected and activated in vitro. After a few days, the activated T-cells are incubated with either a retrovirus or lentivirus supernatant to transfer the CAR gene into the T-cell. Thereafter, expansion and washing of the cells is performed and finally infused back into the patient. Total time for the entire process is about 2 weeks.

Figure 36: Production of CAR T-cells in a GMP facility



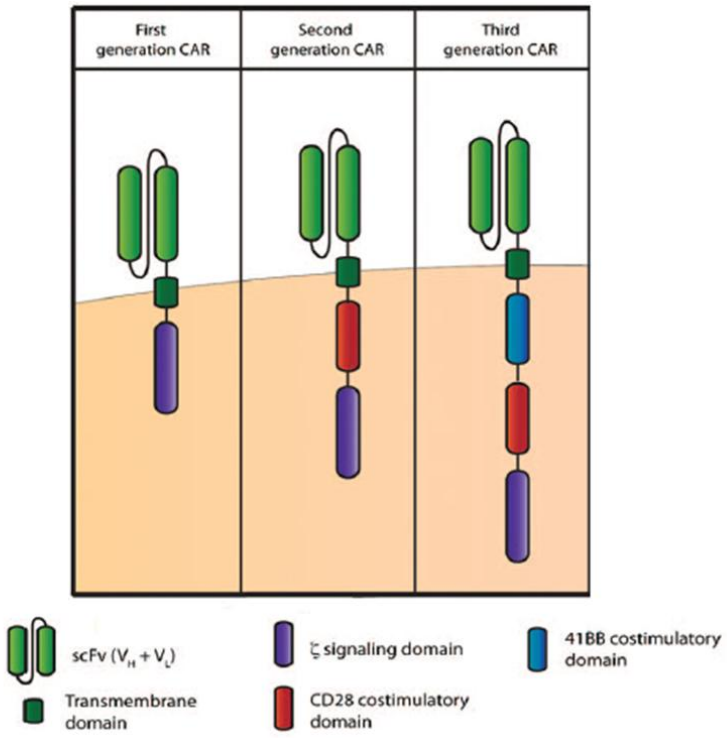
Source: Davila M et al. *Int J Hematol*. 2014

ANATOMY OF CARS AND CAR T-CELL PRODUCTS

The anatomy of CARs reflects on the principle of using gene-transfer technology, with gamma-retroviral and lentiviral vector designs, to efficiently introduce tumor-specific cloned CARs into immune effector cells. With this genetic reprogramming, the effector immune cells (T-cells) are redirected to target antigens expressed on hematologic cells. CARs are composed of an antigen-specific binding domain, or most commonly a single-chain variable fragment (scFv). Individual scFvs, derived from either murine or humanized antibodies, have a high and broad affinity toward specified antigens. The figure below (Brentjens R. et al. Hematology 2012) represents the binding domain of scFv with various signaling domains.

Initial designs of CARs only contained a single cytoplasmic signaling domain derived mostly from the TCR-derived CD3 chain. These "first generation" CARs had only CD3 as an intracellular signaling domain. These CARs obtained a primary activation signal (signal 1) when they encountered the targeted antigen, but the signal was immediately deactivated due to lack of additional costimulations (signal 2) (Savoldo B. 2011). Therefore, institutions addressed this issue by constructing additional T-cell – costimulatory signaling domains (CD28, 4-1BB, or OX-40). These "second generation" CARs, capable of producing both signal 1 and signal 2 when encountering an antigen, resulted in improved response rates in both preclinical and clinical settings. Further developments of "third generation" CARs have been rolled out into clinical trials, with a total of 3 signaling domains for improved antigen response.

Figure 37: CAR technology evolution through the generation of more potent CARs



Source: Brentjens R et al. *Hematology*. 2012

Figure 38: Signaling domain of CAR T-cell therapy

Company	ScFv	Signaling Domain
KITE – NIH	CD19	CD3z – CD28
Novartis – UPenn	CD19	CD3z – 4-1BB
Juno – MSKCC	CD19	CD3z – CD28 / CD3z – 4-1BB
Bluebird – Bayor College	CD19	CD3z – CD28

Source: Clinicaltrials.gov; June et al. *Blood*. 2014

Except for Novartis and Fred Hutchinson of Juno using CD3z – 4-1BB, most institutions use CD3z – CD28 as their costimulatory signaling domain for CAR T-cells to fulfill their antitumor function. Previous studies indicate that inclusion of CD28 significantly increase IL-2 production compared to other molecules (Finney HM. 2004), while other studies show 4-1BB domains have higher CAR-transduced T-cell survival through anti-apoptotic protein Bcl-x (Zhao W. 2009). However, current literature remains conflicting and does not report a clear conclusion on which signaling domain is better than the other.

GENE TRANSDUCTION METHODOLOGY (RETROVIRAL VS. LENTIVIRAL)

Currently, two vector systems, retroviral or lentiviral vectors, can be used to transfer CAR-coded genes into T-cells.

A. Retroviral

Retroviral vectors yield a high level of stable transgene expression through integration into the transcriptionally active site of the host gene. Advantages to the retroviral approach include long-term experience from various clinical trials and permanent gene expression. Currently, KITE, Juno, and Bluebird all use gamma retrovirus as their vectors.

B. Lentiviral

Unlike retroviral vectors, lentiviral are capable of integrating into non-dividing cells, whereas retrovirus can only integrate into efficiently dividing T-cells. Theoretically, integration into undifferentiated T-cells should lead to improved function in vivo. Another advantage of lentivirus is a lower risk of damaging insertions, preventing a "frameshift" to occur to the sequence of amino acids. However, these advantages have yet to be shown clinically. To date, only Novartis uses lentivirus as a vector for transgene expression.

Figure 39: Vectors of CAR T-cell therapy

Company	Vectors
KITE – NIH	Gamma Retrovirus
Novartis – UPenn	Lentivirus
Juno – MSKCC	Gamma Retrovirus
Bluebird – Baylor College	Gamma Retrovirus

Source: Clinicaltrials.gov; June et al. *Blood*. 2014

APPROACHES TO ENHANCE T-CELL EXPRESSION AND EXPANSION IN VIVO

Multiple in vitro approaches have attempted to enhance the effectiveness of T-cells in addition to introducing co-stimulatory agents. Transduction with exogenous IL-2 has been shown to increase T-cell proliferation significantly. Other researchers have looked into enhancing the over-expression of anti-apoptotic proteins like Bcl-2 or Bcl-xL to increase in vivo persistence, as well as down-regulating the immunosuppressive effect of TGF-B.

Another approach to improved T-cell expression is by pre-selecting the best T-cell subset for gene transfer. The differentiation status of genetically engineered T-cells and addition of various supportive cytokines can influence survival of the CARs. Data shows the usage of CARs with central memory phenotype and high percentage of CD4+ T-cells resulted in significantly higher tumor response in neuroblastoma. Additionally, these selected cells expanded and persisted at a low level, making T central memory (TCM) cells highly attractive for adoptive cell transfer. So far, most clinical trials use unselected peripheral blood T-cells, while only few studies use immunomagnetic selection of specific TCM cells.

In vitro activation of T-cells through tissue media has been shown to have significant applications toward in vivo gene transfer. The addition of high doses of IL-2 to culture media induces differentiation toward late effector T-cell states. Reports of co-stimulation with IL-7 and IL-15 may also direct T-cells toward greater in vivo persistence. Therefore, when comparing the technology between companies, the approaches they use for T-cell expansion and survival in vivo is critical in understanding the advances in their technology and may predict their efficacy.

Figure 40: In vitro/in vivo activation of CAR T-cell therapy

Company	Cell Type/Selection
KITE – NIH	IL-2
Novartis – UPenn	T cells from donor
Juno – MSKCC	CD19 CAR-transduced EBV-specific CTLs from donor
Bluebird – Baylor College	Ipilumumab 2 weeks after T cell infusion for expansion

Source: Clinicaltrials.gov

Clinical experience has shown that optimizing cell engineering in vitro is not the only issue that has to be addressed. Moreover, the efficacy of adoptive CAR T therapy can be enhanced by changing the host environment itself prior to T-cell therapy. The reason for this concept is to reduce residual cancer cells prior to CAR T infusion, rising from the data by the MSKCC group showing an inverse correlation between tumor burden and T-cell expression. Various regimens have been used, including non-myeloablative chemotherapy regimens with lymphodepleting activity (cyclophosphamide and fludarabine) or nucleoside analogues like gemcitabine. Additionally, the host environment can also be modified through systemic administration of high-dose IL-2, increasing T-cell expansion in vivo. However, due to significant toxicity from severe vascular leak syndrome, this therapy is currently not used in most trials.

Figure 41: Conditioning regimens of CAR T-cell therapy

Company	Conditioning therapy
KITE – NIH	Fludarabine+Cyclophosphamide
Novartis – UPenn	Cyclophosphamide/Bendamustine Fludarabine + Cyclophosphamide
Juno – MSKCC	Cyclophosphamide
Bluebird – Baylor College	None

Source: Clinicaltrials.gov

NO CORRELATION BETWEEN T-CELL DURATION/DOSE VS. EFFICACY

One of the most controversial topics to date with CAR T-cell therapy is survival of T-cells in vivo and clinical response. The UPenn group hypothesize that persistence of T-cells for at least several months is required based on reported kinetics of tumor clearance that the group observed. However, Kite's DLBCL study had T-cell durations of only 7-17 days, with clinical remissions as long as 22 months. This was again validated in the pediatric/adult relapsed/refractory ALL trial by NCI where 70% CR was seen despite short T-cell duration.

In terms of dose vs. response correlation, the UPenn trial in CLL patients comparing the two dose arms yielded similar efficacy results with no additional benefit in response when higher doses of CAR T-cells were used. It is not yet clear if there is a relationship between the dose of CAR T-cells administered and the level of T-cell engraftment in vivo. When CAR T-cells expand efficiently, very low doses of CAR T-cells can still exert dramatic effects and control tumor. We believe this issue needs to be addressed further with larger, randomized controlled clinical trials.

TOXICITIES – CYTOKINE STORM CORE ISSUE

Despite very high interest in CAR T-cell technology, several recent serious adverse events have been reported in subjects receiving CAR T-cells, warranting safety concerns. Two deaths occurred at MSKCC (partnered with Juno), with the first being a bulky CLL patient developing severe cytokine release syndrome after CAR T-cell therapy and another relapsed ALL patients receiving a second CAR T treatment complicated by severe epilepsy and coma despite being on 3-5 anti-epileptics and anesthesia medications. UPenn also reported similar cytokine storm (fever, tachycardia, hypotension) events with their 4 – 1BB CAR T-cell therapy, though all recovered without sequelae, in some cases, after receiving steroids. Although it is straightforward to hypothesize that CAR T-cells directly kill tumor cells, it is not entirely clear which cell type produces the vast majority of the cytokines, particularly IL-6. Maus et al attributes the upsurge of IL-6 to be produced by the lysis of B-cells and recruitment of macrophages to further digest the lysed cells.

Several patients across institutions have also experienced obtundation, seizures, aphasia, and mental status changes, though all have been reversible. Data has shown that CAR T-cells have been found in the CSF of both symptomatic and asymptomatic patients, leading to the ability to cross the blood brain barrier. Institutions are developing

guidelines to control these reactions, including optimal timing and dose administration of cytokine blockade with tocilizumab (IL-6 inhibitor), corticosteroids, prophylaxis seizure medications, and aggressive sepsis management. However, it is not currently known if interruption of the cytokine cascade by IL-6 inhibitors or steroids leads to interruption of the antitumor effect of the therapy.

The severity of the cytokine storm does appear to be related to the tumor burden (Maus M. 2014). Davila et al showed in a retrospective study of 16 patients with B-cell ALL that pretreatment tumor burden, measured by specific inflammatory cytokines, correlated with severe CRS. However, it has yet to be determined if the severity of the cytokine storm research is actually related to antitumor efficacy.

CURRENT TREATMENT PARADIGMS OF LEUKEMIA/LYMPHOMA

RELAPSED/REFRACTORY DLBCL

DLBCL accounts for approximately 30% of NHLs diagnosed annually, and most patients receive chemotherapy with ~80% ORR in the front-line setting. Immunophenotyping for DLBCL express CD19+, making this disease an excellent target for KTE-C19. Though initial treatment with chemotherapy can have a response rate of as high as 80%, patients who are refractory or relapsed from first line therapy have a poor survival. Second-line therapy is mainly autologous transplant, though most of the patients are too elderly to receive such an intensive regimen. In patients with DLBCL that has progressed after autologous stem-cell transplantation, median OS is less than 10 months.

Among patients with DLBCL refractory to second-line chemotherapy, less than 50% of patients respond to third-line chemotherapy, and few experience long term survival. New therapies include chemotherapy regimens (ICE, DHAP, CHOP, dexaBEAM, and gemcitabine containing regimens) or single agent investigation drugs including lenalidomide, bortezomib, and mammalian target of rapamycin inhibitors. Salvage therapy for DLBCL is broken into patients eligible for autologous stem cell transplant (ASCT) or non-ASCT patients. Though ASCT shows improved efficacy, less than half of the patients are transplant eligible. Additionally, the benefit of ASCT is only ~50%

Figure 42: Treatments for DLBCL

Trial	Regimen	Response
ASCT eligible		
PARMA study	ASCT vs. DHAP	5 year EFS: 46% vs. 12%; OS: 53% vs. 32%
Coral Study	BEAM + ASCT --> Ritux maintenance	3 year EFS: 21% - 47%
	ICE/DHAP prior to ASCT	ORR: 43% (21% CR; 14% PR); median OS: 6 mons
ASCT ineligible		
Ogura M et al	Bendamustine + rituximab	ORR: 45.8% (15.3% CR; 30.5% PR); Median PFS 3.6 mon
Mounier N et al	Rituximab + GemOx	ORR: 83%; 2 year EFS: 43%
Wiernik et al.	Lenalidomide	ORR: 35%; low toxicity
Third line		
	Clinical trial - no standard therapy	

Source: Canaccord Genuity research

Only 25% of relapse/refractory patients are ASCT eligible

For fit patients who are eligible for ASCT, the first goal is to minimize the disease burden and demonstrate chemosensitivity prior to transplant with the use of a non-cross resistant salvage regimen. Although CR is not required, demonstration of response is the most predictive factor of outcome following ASCT. The pivotal CORAL trial studied patients with relapsed DLBCL and the response of ICE or DHAP prior to ASCT. The study showed that chemotherapy regimens produced an ORR of only 43%, with 21% CR rates and 14% PR rates. Median overall survival is only 6 months. Therefore, improved treatments for these patients are clearly needed (Neste E 2013). In the last decade, a major focus has been trying to incorporate radioimmunotherapy into transplant for better efficacy (i.e., tositumomab) as well as maintenance therapy with rituximab post-transplant. Despite these effects, improving ASCT has only limited impact on the outcome of relapsed/refractory DLBCL, as 50% of ASCT patients still relapse or are refractory to the transplant itself. In these patients, prognosis remains very poor, with median survival of ~3 months (Vose JM 1992)

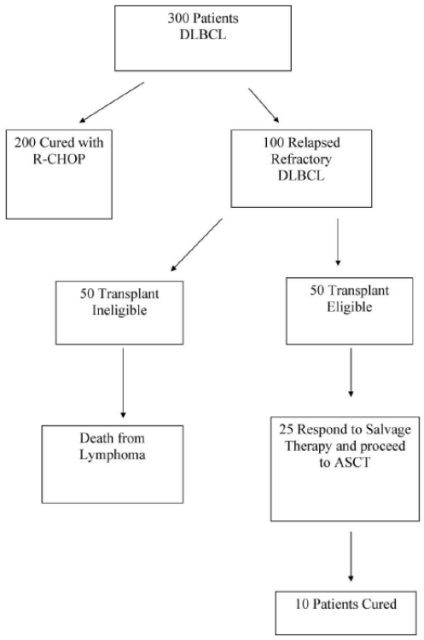
Most patients are ASCT ineligible ~75%

For patients ineligible for ASCT, the outcome remains very poor, with essentially no chance at prolonged disease control. Goals of therapy in this setting are purely palliative since these patients cannot tolerate intensive chemotherapy. Therefore, single agent rituximab is mainly used, showing modest, transient activity in this setting. Lenalidomide has been studied in phase 2 trials with a response rate of 35%, though duration of response remains short.

Third line – poor prognosis

For patients who do not respond to the first salvage regimen, the outcome is extremely poor and cure is very unlikely. In a series of 74 patients from Cornell University with relapsed or refractory DLBCL who underwent second-line chemotherapy, 36% did not respond. Similar to the COAR study, the median OS of these patients was only 4 months, with only 1 patient (4%) surviving up to one year (Elstrom RL 2010). The choice of third-line aggressive chemotherapy did not confer a benefit when compared to less intensive approaches, emphasizing the poor outcome of this group and lack of available treatments.

Figure 43: DLBCL treatment algorithm



Source: Friedberg J. *Hematology.* 2011

RELAPSED/REFRACTORY ALL

Patients with front-line acute lymphoblastic leukemia have a high chance of obtaining CR with intensive induction chemotherapy, nearing ~80-90%. Children have a better prognosis compared to adults, with 80% obtaining PFS in 6 years. However, among the 20% who experience relapse, only ~30% experience long-term remission with subsequent therapies. Adults have a much worse prognosis, with relapse rates of about 40-72% and long-term DFS rates are disappointingly short, lasting only 2-7.5 months in adults.

Goal in relapsed/refractory ALL: Allogeneic Stem Cell Transplant

Retrospective analysis of children and adolescents with pre-B cell ALL experiencing a second CR after bone marrow relapse showed lower risk of relapse and overall mortality when they received HSCT vs. chemotherapy (Eapen M 2006). BFM-87 study confirmed these results, showing 10 year EFS significantly higher among patients who received HSCT after second CR compared with those receiving chemotherapy only (59% vs. 30%). Based on these results, current guidelines from American Society of Blood and Marrow Transplantation (ASBMT) recommend HSCT over chemotherapy alone for adult patients with relapsed ALL if they are able to obtain a second CR. However, the problem for these patients is not optimizing transplant therapy, but rather the ability to obtain a CR prior to HSCT, with only 20-30% of patients experiencing a second CR with second-line therapies.

Clofarabine ~20% response rate

Clofarabine is a nucleoside analog approved for pediatric patients with ALL that is relapsed/refractory to at least 2 prior regimens. Phase 2 studies of single-agent clofarabine achieved a response rate of only 20% (CR+CRp). Combination therapy of clofarabine resulted in more favorable response rates. Results from the GRAAL study showed a CR rate of 44% in relapsed/refractory ALL when combined with dexamethasone, mitoxantrone, etoposide, and asparaginase (Pigneux A 2011). However, grade 3 and 4 toxicities were high, with infection of 58% and liver toxicities of 24%.

Augmented hyper-CVAD ~47% response rate

MD Anderson conducted a phase 2 study evaluating augmented hyper-CVAD (asparaginase, intensified vincristine, and intensified dexamethasone) in relapsed/refractory adult ALL patients. Among evaluable patients, CR rates were 47%, but 30 day mortality rate was 9%. Median remission duration was only 5 months, and median OS was 6.3-10.2 months. Only ~30% of patients were able to proceed to HSCT (Faderi S 2001).

Nelarabine ~31% response rate

Nelarabine is a nucleoside analog that is currently approved for the treatment of patients with T-cell ALL who have relapsed after at least 2 chemotherapy regimens. Phase 2 studies of nelarabine in adults reported CR (CR + Cri) of only 31%. Median DFS and OS were both 20 weeks and the 1 year OS was 28%.

Lipsomal vincristine ~20% response rate

Vincristine sulfate liposome injection (VSLI) is a novel nanoparticle formulation of vincristine encapsulated in sphingomyelin and cholesterol liposomes to allow for delivery of increased doses of vincristine without increasing toxicities. Recent phase 2 study in relapsed/refractory ALL had CR (CR + Cri) rates of only 20%. Median duration of CR was 28 weeks and median OS was only ~5 months.

Novel agents: Inotuzumab ozogamicin (57%) + Blinatumomab (67%) response rate

Other agents are currently being studied in this patient population, showing promising results. Inotuzumab is an anti-CD22 antibody-drug conjugate that has shown CR rates of ~57% in phase 2 studies (Kantarjian H 2012). Amgen's Blinatumomab is a bispecific antiCD3/CD19 monoclonal antibody that showed high CR rates of 67%. Although blinatumomab may illicit favorable response rates with low toxicities, we believe the 28 day continuous infusion will prove cumbersome for patients and practitioners.

RELAPSED/REFRACTORY CLL

Chronic lymphocytic leukemia is an indolent, chemosensitive disease state, with front-line therapies achieving 80-95% ORR (higher in the younger patients). However, this malignancy is an incurable disease and all patients are destined to relapse. The patient population remains very heterogeneous, from patients with indolent disease achieving a prolonged first remission, to patients with resistant disease to fludarabine-based chemotherapy. Most of these patients with aggressive disease have poor prognostic factors that include cytogenetic abnormalities, particularly 17p and 11q deletion, and

molecular mutations like IGHV rearrangement. Since the median age for CLL patients is ~ 70 years old, it is important to tailor second- and third-line therapies based on age and tolerability of intensive chemotherapy

Relapse/refractory CLL in younger patients – high initial ORR

For younger patients or "fit" older patients, the use of combination chemotherapy is recommended due to increased efficacy. The multi-agent, FCR regimen has been shown to induce high response rates in the relapsed/refractory disease setting, achieving ORR ~70-80%. In a phase 2 study evaluating FCR in these patients, ORR was 74% with a CR rate of 30%. Median PFS was ~21 months and the estimated median survival up to 4 years. However, if the patient had fludarabine-refractory disease, ORR was decreased to 56%, with CR only at 7% and OS of only 2-3 years. Toxicities were seen with this multidrug combination, including 56% grade III or IV neutropenia and sepsis in 16%. The PCR regimen showed similar response rates, with ORR of 75% and CR of 25%, though single institution studies reported less febrile neutropenia and better toxicity. Other intensive regimens that have been studied include OFAR, R-HDMP, and BR without any therapy standing out as first-line therapy for relapsed/refractory disease.

Relapsed/refractory CLL in older patients

Unfortunately, older patients cannot tolerate intensive multi-regimen chemotherapies given the prolonged neutropenia and toxicities with these intensive agents. Instead, single agent therapies are mainly used to slow down disease progression while maintaining quality of life. In early phase 2 study, alemtuzumab was shown to induce significant responses in patients who were refractory to fludarabine based therapy in 93 patients. The ORR for single agent was 33%, 2% CRs, and median OS of 16 months (2.5 years for responders). However, treatment for patients who relapse from alemtuzumab becomes very challenging. Ofatumumab is a human CD20 monoclonal antibody with activity in patients with fludarabine-refractory CLL who are also refractory to alemtuzumab. Final analysis from the pivotal international clinical trial resulted with ORR of 51%, median PFS of 5.5 months, and OS of 14-17 months, gaining current FDA approval for CLL refractory to both fludarabine and alemtuzumab. Finally, single agent phase 2 studies with lenalidomide in relapsed/refractory CLL patients showed moderate benefit with ORRs of 32-47% and CR rates of 7-9%. Lenalidomide did show significant benefit in the subgroup of patients with del(11q) mutation, where ORR was 39-47%, though there were degrees of toxicity with tumor flare and tumor lysis syndrome.

Investigational agents have changed the CLL treatment paradigm

In the last few years, rapid advancements in the development of potential new agents have held extreme promise in the treatment of CLL. The launch of small molecule inhibitors of anti-apoptotic proteins and small molecule inhibitors of the B-cell receptor (BCR) signaling pathway have shown to exhibit significant response rates without increasing toxicity. Response rates in relapsed/refractory CLL has improved to as high as 90%, changing the way the disease is currently treated dramatically.

First, PI3K is highly involved in the regulation of cell functions such as cell development, proliferation, survival and migration. Recently, idelalisib (PI3K-delta inhibitor) has demonstrated promising clinical activity in CLL patients. A phase 2 study evaluated idelalisib combined with rituximab or bendamustine in patients with relapsed/refractory CLL. ORR was as high as 84%, with median duration of response for 18 months. BTK

inhibitors have also shown significant benefit in this disease, with ibrutinib demonstrating significant response rates when used both in monotherapy and in combination with standard chemotherapy. A phase 1b/2 trial evaluated single agent ibrutinib in previously untreated/refractory CLL patients. ORR was shown to be 71% in untreated elderly patients (10% CR), 67% in relapsed/refractory patients (3% CR), and 50% in high risk patients. PFS at 22 months was 76-96%, with OS at 22 months between 85-96%. Due to this significant clinical response, ibrutinib is currently undergoing phase 3 trials in previously untreated elderly patients with CLL vs. chlorambucil.

It remains interesting to see the role these new agents will play in the landscape of relapsed/refractory CLL. Currently, response rates remain high with ibrutinib/idelalisib, but we await long-term data to see if patients can maintain their remission for > 2 years.

RELAPSED/REFRACTORY MANTLE CELL LYMPHOMA

Despite recent advances in therapeutic strategies, a large proportion of patients with MCL experience progression after first-line therapy. Currently, there is no consensus for optimal treatment in this setting, and median duration of response in second line and beyond is about 9 months. Overall, clinical evidence from phase 2 cytarabine containing regimens, stem cell transplant, and biological agents all have shown some efficacy, presenting possible suitable treatment options. However, these patients usually have poor prognosis since MLC presents the worst features of both high and low grade NHL. Patients usually have a median survival of only less than 2 years.

Chemoimmunotherapy

Few large clinical studies have investigated the role of chemotherapy in relapsed/refractory MCL. Rituximab has been used as monotherapy in this setting, though current therapeutic strategies comprise the use of this monoclonal antibody in combination with other chemotherapy agents. Forstpointer et al. evaluated 24 patients with MCL, 12 in the second-line setting, treated with R-FCM (rituximab, fludarabine, cyclophosphamide, and mitoxantrone). The investigators found an ORR of 58%, including CR of 29%. Other promising regimens include combinations of rituximab with bendamustine, gemcitabine, and cytarabine, all shown to demonstrate strong mitochondrial damage and reduce the metabolic activity of lymphoma cell lines. A new anti-CD20 monoclonal antibody, GA101, has also been tested in refractory/relapsed MCL. A randomized phase 2 trial showed 4/15 (27%) achieving a response after administration.

Figure 44: Chemotherapy regimen for relapsed/refractory MCL

Study	Treatment	Response	Toxicity
Foran et al.	Rituximab	ORR: 37%; CR: 14%	Grade 3-4 leukopenia 25%
Robinson et al.	Ritux + Bendamustine	ORR: 92%; CR: 42%; PFS 23 mon	Grade 3-4 leukopenia 78%, neutropenia 79%
Rodriguez et al.	Gemcitabine + Ritux + Oxaliplatin	ORR: 85%; CR: 64%; PFS 8 mon	Grade 3-4 thrombocytopenia 35%
Forstpointner et al.	FCM vs. R-FCM	ORR: 46% vs. 58%; CR: 0% vs. 29%	
Carton et al.	GA101 (CD20)	ORR: 27%; CR 13.5%	Grade 3-4 thrombocytopenia 20%

Source: Zaja F et al. *Leukemia & Lymphoma*. 2014

Stem cell transplant

For fit, younger patients, autologous transplant should be considered in all patients who are suitable. Evidence remains conflicting as to the true benefit of autoSCT, where several reports indicate that the efficacy of this therapeutic strategy in patients with relapsed/refractory MCL is less marked than in the front-line setting. Allogeneic stem cell transplant has also been studied, but clinical evidence has suggested the high mortality rate from treatment (30-40%) when patients are undergoing conventional myeloablative regimens makes this regimen less favorable.

Biological Agents

Current biological agents include bortezomib, temsirolimus, everolimus, and lenalidomide. Currently, only bortezomib and temsirolimus are FDA approved for the treatment of relapsed/refractory MCL. The figure below is a summary of some of the clinical studies performed in this disease state, with most having an ORR of 35-55% and minimum CRs. Of note, most of these agents are also used in combination with current regimens. For example, bortezomib has been combined with fludarabine, hyper-CVAD, CHOP, and high-dose cytarabine for increased efficacy. Despite the increased response, most patients still relapse around 6 months, incurring significant toxicity from the multi-agent therapy. At present, only temsirolimus was tested in a phase 3 study that demonstrated its superiority over investigator's choice of therapy.

Figure 45: Biological agents for relapsed/refractory MCL

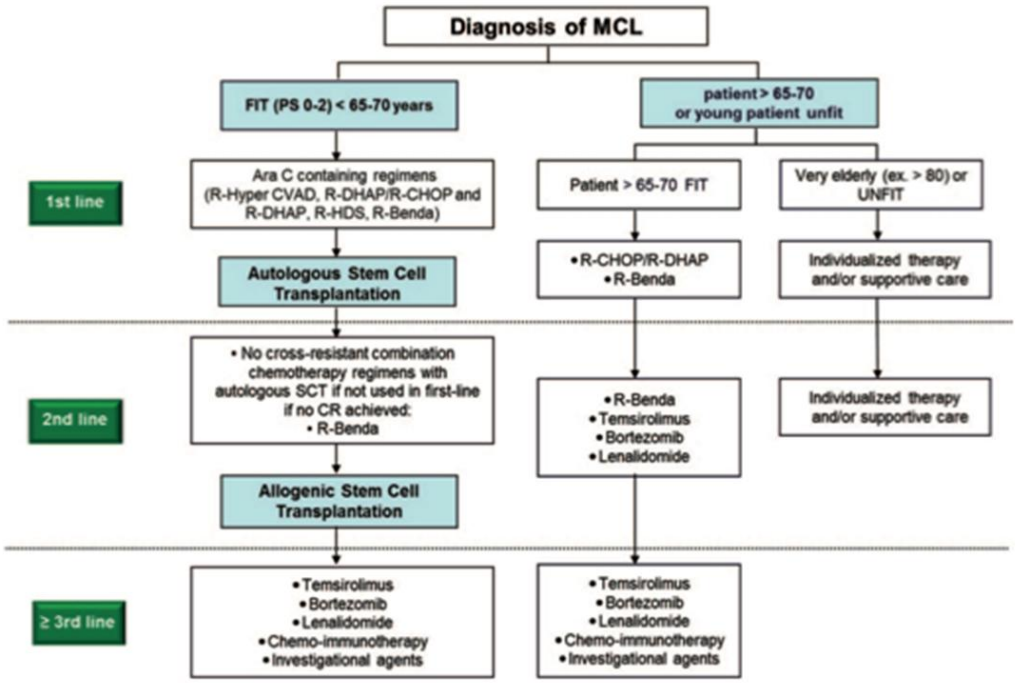
Study	Treatment	Response	Toxicity
Goy et al.	Bortezomib	ORR: 41%; CR: 20.5%; PFS: 6 month – 42%	Grade 3 thrombocytopenia – 47%
Belch et al.	Bortezomib	ORR: 46.4%; CR – 0%	Grade 3 fatigue – 31%
Witzig et al.	Temsirolimus	ORR: 38%; CR – 3%	Grade 3 thrombocytopenia: 65%; anemia 26%; neutropenia 23%
PILLAR-1	Everolimus	ORR: 12%; CR: 0%	Grade 3 anemia – 7%
Habermann et al.	Lenalidomide	ORR: 53%; CR: 20%; PFS: 5.6 mon	Grade 3-4 thrombocytopenia: 13%; neutropenia – 40%
Zaja et al.	lenalidomide + Dex	ORR: 53%; CR: 24%	Grade 3-4 neutropenia: 62%; thrombocytopenia – 42%

Source: Zaja F et al. *Leukemia & Lymphoma*. 2014

Bruton's tyrosine kinase inhibitor (BTK inhibitors) and P13K inhibitors

Phase 2 trials in 111 patients with relapsed/refractory MCL were conducted with ibrutinib. At a median follow-up of 15.3 months, PFS was 13.9 months and ORR was high at 68%. Side effects were limited to only grade 1-2 diarrhea, fatigue and nausea. Preliminary data also suggest the potential effect of targeting the phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR pathway. The treatment of 16 patients with relapsed MCL with CAL-101 – an oral P110δ isoform-selective PI3K inhibitor – resulted in an ORR of approximately 62%.

Figure 46: Treatment algorithm for MCL



Source: Zaja F et al. *Leukemia & Lymphoma*. 2014

The figure above summarizes the clinical options currently available for the treatment of MCL. Patients are stratified into two groups – fit young subjects and elderly/unfit patients. While young, fit patients may be eligible for several treatment strategies, which include stem cell transplant, fit subjects aged between 65–70 and 80 should receive medical therapy only. Very elderly patients or unfit subjects need to be treated with an individualized treatment strategy. From the agents listed above, current therapeutic approaches are still not completely effective in the majority of patients. We eagerly await future trials from Kite in MCL patients, as the bar of success is presently low.

RELAPSED REFRACTORY FOLLICULAR LYMPHOMA

Accounting for 22% of all NHL in the United States, most patients present with advanced stage disease. Although highly treatable with a variety of approaches, including "watch-and-wait" strategy, follicular lymphoma remains incurable and patients are characterized by repeated relapses and retreatments that require an increasing number of active therapies.

Not all patients with relapsed/refractory FL require immediate therapy, since often times patients can be observed until they become symptomatic. Patients can be distinguished into those who are considered to be rituximab sensitive or resistant (disease progression within 6 months following rituximab therapy). If patients relapsed after prolonged response to initial rituximab-containing regimen, rituximab should be included in the next line of treatment, although no consensus on which therapy to use front-line is currently available. Rituximab containing regimens are still commonly used, where ORR of as high as 80% and 30% PFS in 3 years have been reported with RCHOP therapy in second line.

Alternatives to rituximab

90Y-ibritumomab tiuxetan is a radioimmunotherapy (RIT) used in relapsed/refractory FL, achieving responses in 60-80% of patients with a median duration of response of about 1 year, though lower rates have been seen in patients with bulky disease. However, RIT is infrequently used due to high cost, complexity requiring a treating team familiar with the treatment, and the practice of rituximab retreatment. Additionally, RIT has strict exclusionary criteria based on the extent of bone marrow involvement y lymphoma, bone marrow cellularity, and peripheral counts (Zelentz AD 2011).

Bendamustine, a bifunctional alkylating agent, has been commonly used for patients with relapsed/refractory disease. The drug has been found show an ORR of 76%, including CR of 25%, and median duration of response of ~11 months, even in patients considered to have disease refractory to prior alkylating agent therapy. Based on the benefit of single agent bendamustine, combination therapies with rituximab have been added, resulting in greater response rates of >90% and 50-60% CRs, with median PFS of almost 2 years.

New therapies

Currently, there is considerable interest in novel agents that target the cell surface of CD20 after rituximab failure. Ofatumumab, which binds to a different epitope on CD20 than rituximab, was not able to show much benefit where response rates were only 11% in rituximab-resistant patients. However, GA101 (obinutuzumab), a third-generation, glycosylated monoclonal antibody with promising single-agent activity in patients with relapsed/refractory disease, showed promising data when it was compared in patients taking rituximab and GA101 ± placebo. This head-to-head trial comparing GA101 + rituximab showed higher response rates in the GA101 group 43.2% vs. 28% in the rituximab monotherapy group with no appreciable differences in safety.

Drug antibody conjugates involve the linking of a monoclonal antibody capable of being internalized with a toxin. The first such drug was brentuximab vedotin, which was approved for use in Hodgkin lymphoma and anaplastic large T-cell lymphoma. The same liner and toxin, monomethyl auristatin E (MMAE), has been combined with anti-CD22 to form DCDT, which is currently in a phase 1 study. Inotuzumab ozagomicin, which uses

calicheamicin as a toxin that binds to DNA, has also been studied, with response rates in excess of 50% in patients with FL.

Lenalidomide, a second-generation immunomodulatory agent, has been studied to modify the FL's microenvironment. Reports show a response of ~25% monotherapy and the drug is currently being combined with a wide variety of chemotherapeutic and biological agents. The CALGB 50401 study of combining lenalidomide with rituximab vs. lenalidomide alone showed higher ORR (75% vs. 49%) and higher CR (32% vs. 13%) in the combination arm. Median EFS was significantly longer in the combination group as well (2 years vs. 1.2 years; p=0.0063).

Additionally, P13K inhibitors have also been studied in this disease state, where it's been shown that that the P13K signaling pathway is frequently hyperactive in B-cell neoplasms. The safety and efficacy of idelalisib in patients with relapsed indolent NHL was evaluated in a phase 2 study. Among patients with FL, 79% of the patients were intermediate-risk or high-risk disease. The median duration of response was 6.6 months, resulting in ORR of 57%, and 47% of the patients remained progression free at 48 weeks. Based on these results, idelalisib was recently approved by the FDA for the treatment of relapsed FL that has not responded to at least two prior systemic therapies.

Transplant

The role of autologous stem cell transplantation in relapsed or refractory FL is questionable with most studies including highly selected patients. On the other hand, recent data using allogeneic bone marrow transplantation provide evidence for long-term disease-free survival, though treatment related mortality rates were as high as 30-40%. Transplantation of any sort is best offered prior to the patient being heavily treated and demonstrating chemoresistance.

T-CELL RECEPTORS (TCR)

T-cell antigen receptor technology represents a similar approach in immunotherapy when compared to CAR T-cells. TCRs recognize a tumor antigen epitope presented by the major histocompatibility complex (MHC) on the tumor cell along with T-cell activating domains, irrespective of their cellular localization. Benefits of TCR approach have the following advantages:

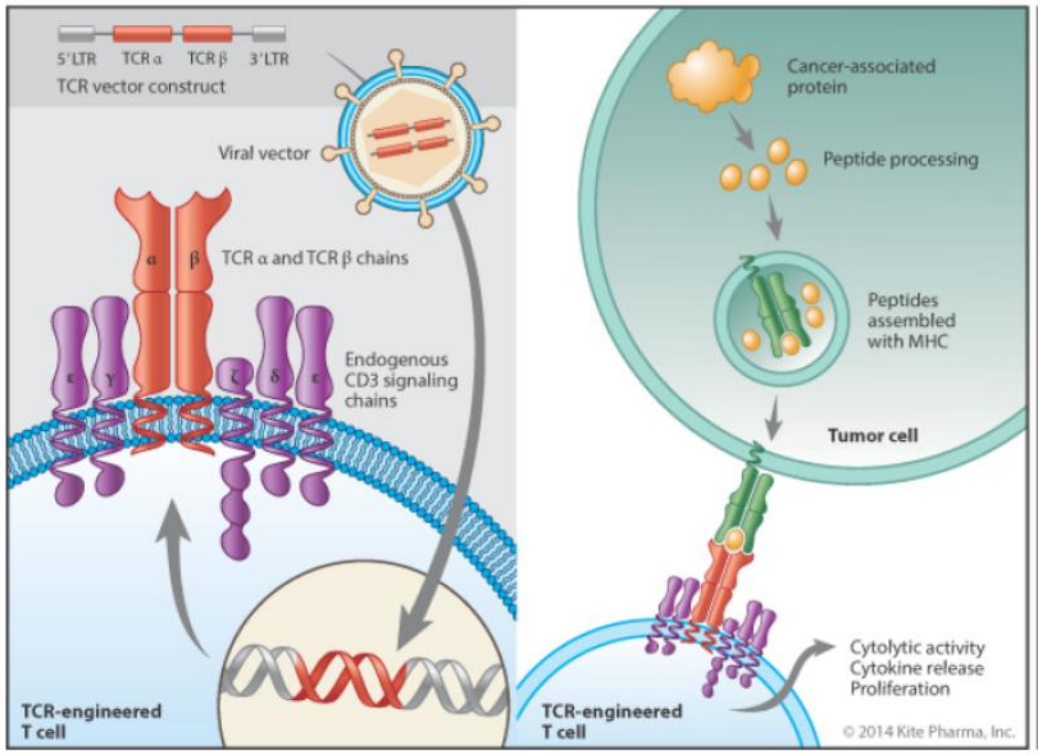
1. Relies on the natural way of T-cell function;

2. Low risk of cytokine release syndrome through low avidity activation;

3. Transduced cells are showing low immunogenicity.

Similar to CAR T-cell therapy, engineering T-cells with TCR involves a similar viral vector to transduce the TCR gene into the T-cells. The TCR protein, designed to bind with specific peptides presented by the MHC on the surface of cancer cells, are expressed on the T-cell surface. Upon binding of TCR to the peptide-MHC complex on the cancer cell surface, the natural components of the T-cell (specifically CD3 proteins) deliver signals that trigger T-cell activation, resulting in direct killing of the cancer cell and stimulation additional anti-tumor cells through cytokine release.

Figure 47: T-cell receptor construct



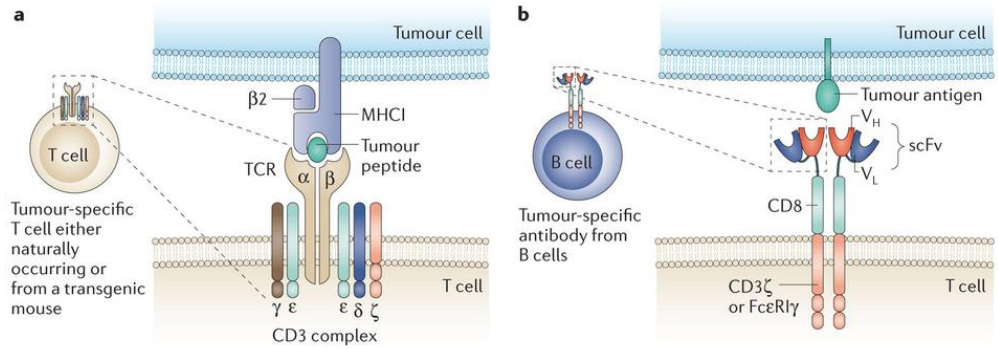
Source: Kite Pharma

TCR targets specific cancer testis antigens (CTAs), which are expressed on a wide variety of common tumor types of various histological origins. KITE is currently pursuing a subset of CTAs, which include SSX2, NY-ESO-1 and MAGE since these antigens are not commonly expressed in normal tissues. However, the main limitation to TCR therapy is the low cell surface expression of TCRs and low affinity for binding. The majority of cancer target proteins are derived from normal proteins in the body and T-cells are naturally not selected to recognize them.

Differences between CAR and TCR

The figure below shows the differences between TCR and CARs. On the left, the TCR genes, made up of both α and β chains, can be derived from tumor-specific T-cells that occur naturally in humans or from HLA-transgenic mice. When the TCR encounters a processed tumor antigen peptide fragment displayed on the MHC of the tumor cell, phosphorylation of immunoreceptors occur, leading to downstream cascade of intracellular signaling and cytokine/cytotoxic effects.

Figure 48: Derivation of TCRs and CARs for the genetic modification of T-cells



Source: Kershaw M et al. *Nature* 2013

The right hand side of the figure represents the CAR T-cell, composed of the single-chain antibody variable fragment (scFv) extracellular domain. This scFv is linked to a CD8 hinge to transmembrane cytoplasmic signaling regions derived from various costimulatory agents. Therefore, the differences are due to three fundamental aspects:

A. MHC Restriction

TCRs only recognize peptides in the context of MHC molecules expressed on the surface of tumor cells. Therefore, TCR-based product candidates must be matched to the human MHC molecules (known as HLA protein). CAR T-cells are not MHC-restricted and possibly have a wider spectrum

B. Cancer Target Frequency

Although CAR T-cells are not HLA-restricted, the technology is limited by the low number of antibody targets available to re-direct the T-cells, where only 20-30% of all encoded proteins may be extracellular. TCRs have a broader therapeutic approach because they recognize specific peptides that are intracellular, which reflects >80% of cancer targets that's not available to the antibody approach.

C. Antigen-presenting Cell Recognition

Unlike CARs, TCRs can also recognize cancer antigens that are not directly on the tumor cells, but also on the surface of antigen-presenting cells in the tumor microenvironment. These cells include dendritic cells, macrophages, and certain B-cells. This broadens the range of targets for TCRs, potentially amplifying the immune response as well.

Current NCI phase 1-2a and phase 2 trial

Kite is currently funding a phase 2 clinical trial involving TCR-based T-cell therapy targeting NY-ESO-1 antigen. The primary objective is to determine whether the administration of anti-NY-ESO-1 plus IL-2 following nonmyeloablative lymphoid depleting preparative regimen may result in tumor regression in cancers expressing NY-ESO-1 antigen. Secondary endpoints are to determine the in vivo survival of the gene engineered cells and determine the toxicity profile of this treatment regimen. No results have been presented to date.

The NCI phase 1-2a clinical trial of TCR based therapy targeting the MAGE antigen is being conducted with one patient enrolled to date. Primary objectives are to determine

safety and tumor regression of the MAGE-antigen TCR following nonmyeloablative/lymphodepleting preparative regimen. Patients are currently being enrolled into the phase 1 dose escalation part of the trial and no results from this trial are currently available.

A planned NCI phase 1-2a trial of TCR-based therapy targeting the SSX2 antigen has not yet begun.

EGRFVIII CAR INTERESTING IN GLIOBLASTOMA

Kite is expanding the CAR T-cell technology into glioblastoma, which we find interesting since all CAR T-cell therapies focus on B-cell malignancies. The company plans on using its technology on epidermal growth factor variant III (EGFRvIII), the most common mutation (~30-67%) found in only glioblastoma and not in normal tissues, and plans on filing IND in 2016.

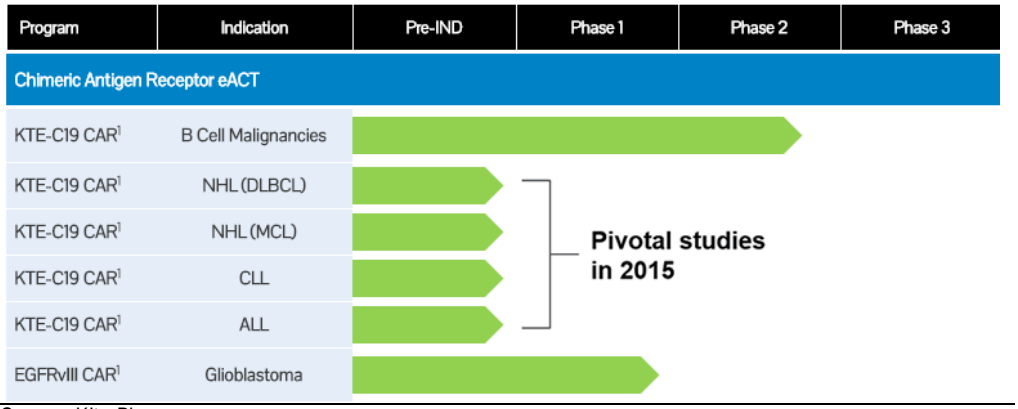
Recurrent glioblastoma extremely poor prognosis

Glioblastoma is the most aggressive primary brain tumor, comprising 51% of all gliomas. Standard treatment, involving resection, radiation, and chemotherapy, maintains a median overall survival of only 14.6 months. Unfortunately, once patients relapse, therapeutic options are severely limited, with best supportive care being the mainstay option. Bevacizumab was previously studied in 154 randomized patients combined with irinotecan. Overall response rates were 37.8%, but median overall survival was ~9 month (Kreisl et al 2011).

Genetically Modified T-Cells Targeting EGFRvIII

NCI is currently using CARs produced from human monoclonal antibody 139, which specifically recognizes glioma stem cell lines and glioma cell lines expressing mutant EGFRvIII. The purpose of this phase 1/2 study in patients with recurrent gliomas is to assess safety and efficacy, determined by 6 month PFS. Secondary objectives are to determine the in vivo survival of CAR gene-engineered cells and radiographic changes after treatment. We believe that positive data could prove interesting given the deficiency of treatments in this disease group, potentially adding another revenue driver for the company.

Figure 49: KITE CAR T-cell pipeline



Source: Kite Pharma

INTELLECTUAL PROPERTY

Cooperative Research and Development Agreement with the NCI

In August 2012, Kite currently has a CRADA agreement (five-year term expiring on August 30, 2017) with the NCI for the research and development of eACT-based product candidates for the treatment of multiple advanced metastatic indications. Under the CRADA, the NCI develops and tests multiple CAR- and TCR-based product candidates targeting various antigens such as CD19, SSX2, NY-ESO-1, MAGE and EGFRvIII. Though each party individually owns all inventions and data, the collaboration provides Kite with an option to negotiate commercialization licenses from the NIH to intellectual property relating to CAR and TCR based products. Kite may exercise this right by providing four-months written notice, and then have ten months to negotiate the license with the NIH. The company is required to make quarterly payments of $250,000 to the NCI for support of research activities.

2013 and 2014 NIH License Agreement

In pursuant to a patent license agreement with the NIH, KITE holds an exclusive, worldwide license to certain intellectual properties, including:

1. CAR-based product candidate that targets CD19;

2. CAR-based product candidate that targets the EGFRvIII antigen for the treatment of brain cancer, head and neck cancer and melanoma;

3. TCR-based product candidate that targets CTA SSX2 for head and neck cancer, hepatocellular carcinoma, melanoma, prostate cancer and sarcoma;

4. TCR-based product candidates that target the NY-ESO-1 antigen for the treatment of any NY-ESO-1 expressing cancer.

Kite is required to make performance-based payments upon successful completion of clinical and regulatory benchmarks relating to the licensed products, aggregating up to

~$4M and possible royalties on net sales of products covered by the license at rates in the mid-single digits.

Cabaret License Agreement

Kite currently has a worldwide license agreement, including the right to grand sublicenses, with Cabaret Biotech Ltd., to certain intellectual property and know-how owned or licensed by Cabaret, including rights associated with KTE-C19. This extensive umbrella patent agreement holds licenses from Weizmann Institute of Science, UCSF, CellGenesis, NCI, and Dr. Zelig Eshhar, covering the concept of combining a single chain variable with T-cells. Since Kite is the first to patent this license, we believe future competitors may enable patent infringement on Kite's KTE-C19 product.

Kite is required to make milestone payment upon successful completion of clinical and regulatory milestones to each product covered by this license, aggregating to ~$3.9M. In addition, royalties will be paid on net sales of licensed products at rates in the mid-single digits.

FINANCIAL OVERVIEW

The company currently has net proceeds of $134.1M as a result of an IPO of 8,625,000 shares of common stock in June 2014. As of June 30, 2014, the company has 38.3 million shares outstanding and cash balances of $203.4M. The company currently has no debt.

Figure 50: KITE Income Statement

($000's) [FY - DEC]	2012 A	2013A	1Q14A	2Q14A	3Q14E	4Q14E	2014E	2015E	2016E	2017E	2018E	2019E	2020E
Revenues													
CAR T-cells													
US			-	-	-	-	-	-	-	263,453	795,983	1,176,814	1,255,539
Ex-US			-	-	-	-	-	-	-	179,806	516,481	800,327	1,031,009
Ex-US royalty			-	-	-	-	-	-	-	26,971	77,472	120,049	154,651
Total revenues	-	-	-	-	-	-	-	-	-	290,423	873,455	1,296,863	1,410,191
Income Statement ($000's)	2012 A	2013A	1Q14A	2Q14A	3Q14E	4Q14E	2014E	2015E	2016E	2017E	2018E	2019E	2020E
Total revenues	-	-	-	-	-	-	-	-	-	290,423	873,455	1,296,863	1,410,191
Cost of goods sold	-	-	-	-	-	-	-	-	-	52,691	159,197	235,363	251,108
Gross profit	-	-	-	-	-	-	-	-	-	237,733	714,259	1,061,500	1,159,083
Operating expenses													
Research and Development	1,802	5,071	2,062	7,424	7,498	7,573	24,557	46,946	47,885	59,857	74,821	93,526	116,908
SG&A	770	1,339	1,070	3,668	3,705	3,742	12,184	15,345	16,112	16,273	16,924	17,601	18,305
Depreciation and amortization	9	17	30	48			78	-					
Total Operating Expense	2,581	6,427	3,162	11,140	11,203	11,315	36,820	62,291	63,997	76,130	91,745	111,127	135,213
Depreciation and amortization	9	17	30	48			78	-					
EBITDA	(2,572)	(6,410)	(3,132)	(11,092)	(11,203)	(11,315)	(36,742)	(62,291)	(63,997)	161,603	622,514	950,373	1,023,870
Operating income (EBIT)	(2,581)	(6,427)	(3,162)	(11,140)	(11,203)	(11,315)	(36,820)	(62,291)	(63,997)	161,603	622,514	950,373	1,023,870
Non-operating Interest income	36	52	-	47	741	696	1,483	2,281	2,044	2,994	7,157	14,574	23,858
Other income/interest expense	(27)	13	21	(6,266)									
Pre-tax income (EBT)	(2,571)	(6,362)	(3,141)	(17,359)	(10,462)	(10,619)	(35,337)	(60,010)	(61,953)	164,597	629,671	964,947	1,047,728
Provision for Income Taxes	-	-	-	-	-	-	-	-	-	60,901	232,978	357,031	387,659
Net Income	(2,571)	(6,362)	(3,141)	(17,359)	(10,462)	(10,619)	(41,582)	(60,010)	(61,953)	103,696	396,693	607,917	660,069
Preferred Dividends		1,436	557	532									
Net Income to Common Shareholders	(2,571)	(7,797)	(3,698)	(17,891)									
Adjustments to Net income													
GAAP EPS	(0.48)	(1.42)	(0.66)	(2.27)	($0.28)	($0.28)	($1.85)	($1.49)	($1.48)	$2.23	$7.62	$10.43	$10.11
Adjusted EPS excl options expense													
Diluted Weighted Average Shares	5,314,214	5,473,384	5,571,499	7,890,029	38,000,000	38,380,000	22,460,382	40,321,006	41,841,712	46,484,917	52,063,107	58,310,680	65,307,962

Source: Canaccord Genuity

Figure 51: KITE Valuation

Product	Peak Sales/Royalty ($MM)	Year	NPV at launch	Estimated launch	Time to launch	Probability Adjustment	Current Value ($MM)	Value / Share
KTE-C19								
US								
DLBCL US	$691	2020	$2,970	10/1/2017	2.9	30%	$654	$17
CLL US	$83	2021	$327	10/1/2018	3.9	30%	$65	$2
ALL US	$195	2021	$979	10/1/2018	3.9	30%	$194	$5
FL US	$165	2021	$736	10/1/2018	3.9	30%	$146	$4
MCL US	$164	2021	$732	10/2/2018	3.9	30%	$145	$4
US - total	**$1,298**	**2020**	**$5,744**	**10/1/2017**	**2.9**	30%	**$1,264**	**$33**
Ex-US								
DLBCL royalty Ex-US	$53	2020	$508	6/1/2018	3.6	30%	$104	$3
CLL royalty Ex-US	$6	2021	$56	6/1/2019	4.6	30%	$10	$0
ALL royalty Ex-US	$15	2021	$142	6/1/2019	4.6	30%	$26	$1
FL royalty Ex-US	$13	2021	$110	6/2/2019	4.6	30%	$20	$1
MCL royalty Ex-US	$12	2021	$109	6/3/2019	4.6	30%	$20	$1
Ex-US - royalty - total	**$99**	**2020**	**$994**	**6/1/2018**	**3.6**	30%	**$204**	**$5**
Total Product Value							**$1,407**	**$37**
Cash							$200	$5.3
Total Equity Value							**$1,607**	**$42**
Shares Outstanding (MM)							38	

Risk-Free Rate	3.0%
Beta	1.8
Risk Premium	5%
Discount Rate	11%

Source: Canaccord Genuity

Investment risks

Although NCI is conducting a phase 1-2a trial of anti-CD19 CAR T-cell therapy, KITE's KTE-C19 trial has not begun. Any delays or significant negative results from NCI's clinical trials could negatively affect Kite's IND application and delay the timing to start their own phase 1-2 clinical trial.

KITE is highly dependent on the third parties for R&D and early clinical testing of CAR and TCR product candidates. These collaborations related to the intellectual property licensed from the NIH relating to product candidates targeting the EGFRvIII antigen, the SSX2 antigen and the NY-ESO-1 antigen and from Cabaret for intellectual property relating to KTE-C19.

The differences in manufacturing compared to NCI may render the product incomparable, particularly with respect to clinical trials, which could negatively affect our valuation. Although plans for manufacturing and processing is based on current approach undertaken by the NCI, the company cannot ensure that even minor changes in the product process will not result in significantly different T-cells that may not have similar efficacy or toxicity.

KTE-C19 could fail in clinical studies, resulting in significant downside to our price target and shares of the stock.

Kite faces significant competition from other biotechnology and pharmaceutical companies in the space of immunotherapy, including Novartis, Juno, Bluebird, Cellectis and Adaptimmune, as well as companies developing novel targeted therapies for cancer.

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Site Visit: An analyst has not visited Kite Pharma's material operations.

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Kite Pharma	5, 7

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