NOVARTIS

ONCOLOGIC DRUGS ADVISORY COMMITTEE BRIEFING DOCUMENT

Tisagenlecleucel (CTL019)

for the

TREATMENT OF PEDIATRIC AND YOUNG ADULT PATIENTS WITH RELAPSED/REFRACTORY B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

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List of abbreviations

AE	adverse event
AESI	adverse event of special interest
ALL	acute lymphoblastic leukemia
allo-SCT	allogeneic stem-cell transplantation
ALT	alanine transaminase
anti-mCAR19	anti-murine CAR19 antibodies
AST	aspartate transaminase
AUC0-28d	exposure or levels of transgene attained during the initial 28 days following infusion of tisagenlecleucel
AUC0-84d	exposure or levels of transgene attained during the initial 84 days following infusion of tisagenlecleucel
BLA	Biologics License Application
BOR	best overall response
CAR	chimeric antigen receptor
CI	confidence interval
CLL	chronic lymphocytic leukemia
Cmax	maximum (peak) expansion of transgene post-tisagenlecleucel infusion
CNS	central nervous system
CR	complete remission
CRi	complete remission with incomplete blood count recovery
CRS	cytokine release syndrome
CV	coefficient of variation
DIC	disseminated intravascular coagulation
DoR	duration of remission
EAS	Efficacy Analysis Set
EFS	event-free survival
EQ VAS	EuroQol visual analogue scale
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
GvHD	graft-versus-host disease
GxP	Good X Practice
HCPs	healthcare providers
HHV-6	human herpes virus-6
HLH	hemophagocytic lymphohistiocytosis
HRQoL	health-related quality of life
ICU	intensive care unit
IFN	interferon
Ig	immunoglobulin
IL	interleukin
IND	Investigational New Drug
IRC	Independent Review Committee
MAS	macrophage activation syndrome

MCL	mantle-cell lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
NE	not estimable
NR	no response/non-responder
ORR	overall remission rate
OS	overall survival
PedsQL	pediatric quality of life inventory
Penn	University of Pennsylvania
PPS	Per-protocol Set
PRO	patient-report outcome(s)
QoL	quality of life
qPCR	quantitative polymerase chain reaction
RCL	replication-competent lentivirus
REMS	Risk Evaluation and Mitigation Strategy
r/r	relapsed/refractory
SAE	serious adverse event
SCT	stem-cell transplantation
SMQ	standard MedDRA query
Tlast	time of last observed quantifiable transgene
Tmax	time to reach maximum (peak) transgene concentration
TLS	tumor lysis syndrome
ULN	upper limit of normal
US	United States
WBC	white blood cell

1 Executive summary

1.1 Tisagenlecleucel (CTL019)

1.1.1 Targeted indication

Novartis is currently seeking approval of tisagenlecleucel (CTL019) for the:

- Treatment of pediatric and young adult patients 3 to 25 years of age with relapsed/ refractory (r/r) B-cell acute lymphoblastic leukemia (ALL)

1.1.2 Unmet medical need for r/r B-cell ALL

Despite current treatment modalities, approximately 620 pediatric and young adult patients with ALL relapse each year in the United States (US) after achieving an initial response (Maude et al 2015). The prognosis for patients who relapse is dismal, especially for individuals with ≥ 2 relapses or those who relapse following allogeneic stem-cell transplantation (allo-SCT). Available treatment options fail to markedly improve survival or provide a long disease-free interval; furthermore, these treatments are associated with extensive toxicity.

Although primary induction failure is rare at presentation, occurring in only 2% to 3% of patients, refractory ALL also remains a therapeutic challenge (Ceppi et al 2016).

1.1.2.1 Currently available treatment options for r/r B-cell ALL

Treatment options for pediatric and young adult patients with r/r B-cell ALL include:

- Cytotoxic chemotherapy
  - Data from the pivotal Phase-II study (N=61) of the approved agent, clofarabine, showed an overall remission rate (ORR) (complete remission [CR] and CR without platelet recovery [CRp]) of 20%, with a median duration of remission (DoR) for responding patients of 29 weeks (range: 1 to 48). Median overall survival (OS) was 13 weeks (range: 1 to 89) (Jeha et al 2006). Due to the limited efficacy observed with single-agent clofarabine, several small clinical studies assessed the combination of clofarabine with cyclophosphamide and etoposide (Locatelli et al 2009, Hijiya et al 2011); marginal clinical benefit was observed with these combinations.
- Targeted therapies
  - In a Phase-I/II dose-defining study (N=70) of the CD19/CD3 bispecific T-cell engager, blinatumomab, 32.9% of patients achieved CR or CR with partial hematological recovery (CRh) within the initial 2 cycles in the Phase-II component, and 43.5% of responding patients achieved CR with negative minimal residual disease (MRD). Median OS was 7.5 months (von Stackelberg et al 2016).
- Investigative agents
- Supportive care with non-curative palliative goals

Despite these current treatment modalities (which are mainly used as a bridge to allo-SCT), maintaining a remission in relapsed patients is difficult, and the prognosis for patients with r/r disease remains poor. Allogeneic SCT is a potentially curative option but eligibility is dependent upon both disease and patient characteristics and treatment is associated with

significant morbidity and mortality (see Section 2.2.2). No effective therapies are currently available following allo-SCT. Innovative treatments are urgently needed for the treatment of r/r B-cell ALL to provide deep and durable remissions, to prolong survival, and to improve quality-of-life (QoL). Novel definitive approaches are therefore needed.

1.1.3 Mechanism of action

Tisagenlecleucel is an adoptive immunocellular cancer therapy that uses autologous peripheral blood T cells which have been reprogrammed with a transgene encoding a chimeric antigen receptor (CAR) to identify and eliminate CD19-expressing malignant and non-malignant cells. The CAR is comprised of a murine single-chain antibody fragment which recognizes CD19 and is fused to intracellular signaling domains from 4-1BB (CD137) and CD3-zeta. The CD3-zeta component is critical for initiating T-cell activation and anti-tumor activity while 4-1BB enhances the expansion and, importantly, the persistence of tisagenlecleucel. Upon binding to CD19-expressing cells, the CAR transmits a signal to promote T-cell expansion, activation, target cell elimination, and persistence of tisagenlecleucel. The transduced T cells expand in vivo to engage and eliminate CD19-expressing cells and may exhibit immunological endurance to help support long-lasting remission.

1.1.4 Manufacturing process

The key steps in the tisagenlecleucel manufacturing process can be summarized as follows:

- Patients undergo leukapheresis to collect their blood mononuclear cells; these are cryopreserved and shipped to the manufacturing facility using a dedicated courier service
  - Each leukapheresis is assigned to a dedicated team who only work on a single product at a time
- After thawing, cells undergo a procedure to remove cells detrimental to CAR transduction and growth (i.e. monocytes and B-lineage lymphoblasts) and to enrich for T cells
- T cells are activated ex vivo with anti-CD3/CD28 antibody-coated beads and transduced with a self-inactivating minimal lentiviral vector containing the anti-CD19 CAR transgene
- Transduced T cells are subsequently expanded ex vivo and then washed, formulated, and cryopreserved
- Full release testing is completed prior to release of the cryopreserved final product. Cells are then shipped to the clinical site.

Patients undergo bridging chemotherapy as needed to control their leukemia while the transduced T cells are being manufactured and subsequently receive lymphocyte-depleting chemotherapy immediately prior to tisagenlecleucel infusion.

1.2 Pediatric and young adult r/r B-cell ALL clinical development program

Encouraging data (in the form of durable anti-tumor efficacy) were generated in a single-center Phase-I/IIa trial (Study B2101J; Grupp et al 2013, Maude et al 2014) conducted at the Children's Hospital of Philadelphia (with a first-patient first-visit date of 15-Mar-2012). These results led to the initiation of further trials to evaluate the safety and effectiveness of

tisagenlecleucel in both multicenter (Study B2205J; US) and international (Study B2202; US, Canada, European Union [EU], Australia, and Japan) settings.

The efficacy and safety of tisagenlecleucel were evaluated in these 3 trials involving over 150 pediatric and young adult patients with r/r B-cell ALL, with a maximum follow-up extending to 40.5 months in Study B2101J (Table 1-1). These data were summarized in the Biologics License Application (BLA) and submitted to the US Food and Drug Administration (FDA) on 02-Feb-2017.

Table 1-1 Pediatric and young adult r/r B-cell ALL clinical development program

Study no.	Population, study design, and objectives	No. of patients	Tisagenlecleucel dose	Endpoints
Supportive trials				
B2101J	Single-arm, open-label, US, single-center, Phase-I/IIa trial Safety, tolerability, and engraftment potential	Enrolled: N=71 Infused: N=55	Split dosing Up to a total dose of 1.5×10^7 to 5×10^9 total T cells (0.3×10^6 to 1.0×10^8/kg)	Primary: Safety, feasibility of manufacture, and persistence [1] Secondary: IRC-assessed ORR
B2205J	Single-arm, open-label, US, multicenter, Phase-II trial Efficacy and safety	Enrolled: N=35 Infused: N=29	Single infusion ≤ 50 kg: 0.2 to 5.0×10^6 transduced viable T cells/kg >50 kg: 0.1 to 2.5×10^8 transduced viable T cells	Primary: IRC-assessed ORR Secondary: MRD, DoR, BOR, EFS, OS, safety
Pivotal registration trial				
B2202	Single-arm, open-label, international, multicenter, Phase-II trial Efficacy and safety	Enrolled: N=88 Infused: N=68	Single infusion ≤ 50 kg: 0.2 to 5.0×10^6 transduced viable T cells/kg >50 kg: 0.1 to 2.5×10^8 transduced viable T cells	Primary: IRC-assessed ORR Secondary: MRD, DoR, BOR, EFS, OS, safety, PRO

ALL Acute lymphoblastic leukemia; BOR Best overall response; DoR Duration of remission; EFS Event-free survival; IRC Independent Review Committee; MRD Minimal residual disease; ORR Overall remission rate; OS Overall survival; PRO Patient-reported outcomes; r/r Relapsed/refractory

[1] Cellular kinetics and duration that the transgene or surface expression of tisagenlecleucel is measured

Tisagenlecleucel was initially manufactured using the University of Pennsylvania (Penn) manufacturing process in Studies B2101J and B2205J. Subsequent collaboration between Penn and Novartis led to the transfer of this process to the Novartis facility in Morris Plains, NJ. The manufacturing process and analytical testing were further developed to deliver a consistent process in terms of product quality as determined by testing for appearance, identity, purity, quantity, potency, and safety of the product. The Novartis manufacturing process was also transferred to the Fraunhofer-Institut für Zelltherapie und Immunologie, Leipzig, Germany, for EU-manufactured product.

Evidence of the clinical efficacy of tisagenlecleucel is based primarily on data from the pivotal, single-arm, international, multicenter, Phase-II Study B2202, which utilized tisagenlecleucel manufactured in accordance with the Novartis manufacturing process (with 63 patients worldwide receiving US-manufactured product and 5 patients from the EU receiving EU-manufactured product). Additional data were generated in supportive Studies B2101J and B2205J (Table 1-1).

1.2.1 Trial designs and conduct

Consensus was reached with the US FDA as to the overall design and endpoints of the pivotal trial (Study B2202).

All patients in Study B2202 had CD19-positive B-cell ALL with morphologic marrow tumor involvement at registration (≥ 5% lymphoblasts), with disease that had relapsed or was refractory to treatment. Patients were also required to be either ineligible for, or have relapsed after, allo-SCT. Following assessment of eligibility, patients qualifying for the trial were enrolled. Prior to tisagenlecleucel infusion, a lymphodepleting chemotherapy cycle was planned. After the tisagenlecleucel product was manufactured and the patient fulfilled the protocol-defined safety criteria for the infusion, a single dose of tisagenlecleucel was infused.

The primary endpoint of Study B2202 was ORR, i.e. the proportion of patients with a best overall response (BOR) of CR or CR with incomplete blood count recovery (CRi), as assessed by an Independent Review Committee (IRC) within 3 months post-tisagenlecleucel infusion. The primary efficacy analysis involved testing the null hypothesis of whether ORR within 3 months was ≤ 20% at an overall one-sided 2.5% level of significance vs. the alternative hypothesis of ORR >20%; the 20% threshold was derived from the earlier clofarabine pivotal study (reflecting available data at the time that the trial was designed) (Jeha et al 2006). With the planned sample size, Study B2202 provided >95% overall power to reject the null hypothesis, assuming a true ORR ≥ 45%.

Key secondary endpoints were ORR within 3 months for US-manufactured product, BOR of CR or CRi with an MRD-negative bone marrow (i.e. MRD <0.01%) based on all manufacturing facilities within this 3-month period, and BOR of CR or CRi with an MRD-negative bone marrow for US-manufactured product. These endpoints were to be tested sequentially once the primary endpoint was met.

A planned interim analysis was performed on all data reported up to and including the 17-Aug-2016 data cut-off (with a 01-Nov-2016 database lock), and corresponded to when the first 50 patients administered tisagenlecleucel had completed 3 months of follow-up or had discontinued for any reason. This cut-off included data from patients with US-manufactured product only.

A subsequent analysis was conducted once these initial 50 patients had completed 6 months of follow-up, at the request of FDA. This analysis also corresponded to the final analysis of ORR for US-manufactured product (a secondary endpoint) and had a 23-Nov-2016 data cut-off date and a database lock date of 19-Jan-2017. Unless specified otherwise, all data from Study B2202 presented in this Briefing Document are reflective of this more recent analysis.

Studies B2202 and B2205J had near-identical study designs, and enrolled similar patient populations. Study B2101J was a Phase-I/IIa trial designed to assess the long-term persistence, in vivo proliferation, anti-tumor activity, and safety of tisagenlecleucel in patients with r/r and incurable B-cell malignancies (Table 1-1).

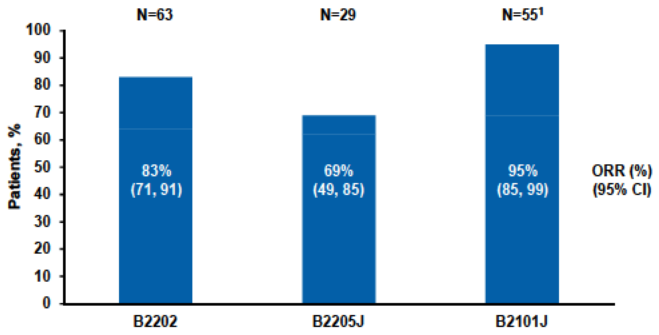
1.3 Efficacy of tisagenlecleucel in B-cell ALL

Results across the 3 trials in the program provided compelling evidence for the efficacy of tisagenlecleucel in the treatment of pediatric and young adult patients with r/r B-cell ALL, with

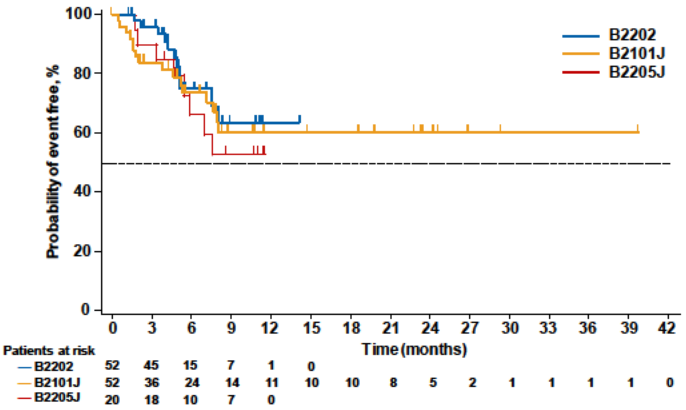
high remission rates (range: 69.0% to 94.5%) and deep (MRD-negative bone marrow) and durable remissions reported (Figure 1-1). Robust and consistent data were generated from these studies to support the efficacy of tisagenlecleucel.

Figure 1-1 Results across pediatric and young adult r/r B-cell ALL program

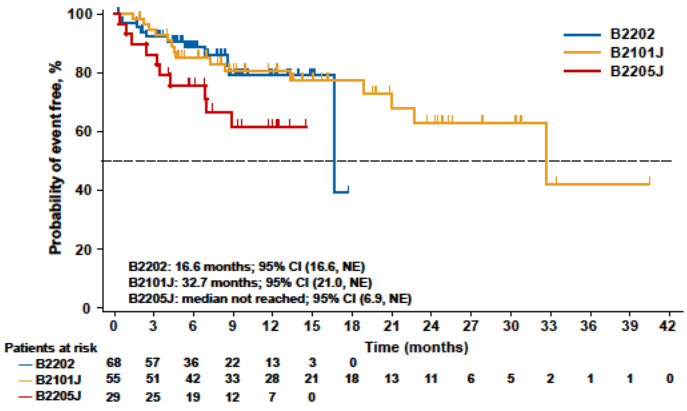
Overall remission rate



Duration of remission



Overall survival



ALL Acute lymphoblastic leukemia; CI Confidence interval; CNS Central nervous system; NE Not evaluable

[1] Overall remission rate (ORR) at Day 28 in patients with non-CNS3 ALL (i.e. no CNS disease involvement)

Results from Study B2202 in the figures above correspond to the final analysis of ORR in patients treated with US-manufactured product

Study B2101J was the first trial to establish the feasibility of tisagenlecleucel manufacturing and treatment of pediatric patients with r/r B-cell ALL with tisagenlecleucel. Transduced T cells were detectable for up to 780 days (at the time of the data cut-off) thus demonstrating the persistence of tisagenlecleucel and its link to long-lasting remission.

Study B2205J and the pivotal registration trial, Study B2202, subsequently showed that tisagenlecleucel administration was feasible in a multicenter setting, with the majority of patients (77.3% in Study B2202 with the infusion pending in a further 4.5% at the time of the data cut-off) able to undergo tisagenlecleucel infusion after meeting the enrollment criteria.

1.3.1 Interim analysis – Study B2202

Results of the interim analysis, conducted when the initial 50 patients had completed 3 months of follow-up or had discontinued for any reason (corresponding to a 17-Aug-2016 data cut-off), indicate that the study met its primary endpoint of ORR:

- ORR per IRC assessment was 82.0% (95% confidence interval [CI]: 68.6, 91.4; p<0.0001)
  - Investigator assessments of ORR were 100% concordant with the IRC analyses

Key secondary endpoints were supportive of the primary endpoint:

- As of the data cut-off date for this interim analysis, all tisagenlecleucel product was manufactured at the Morris Plains facility, NJ. The results of the first key secondary endpoint (ORR within 3 months in patients treated with US-manufactured product) were therefore identical to the primary efficacy endpoint while the results of the third key secondary endpoint (BOR of CR or CRi with an MRD-negative bone marrow in patients treated with US-manufactured product within this 3-month period) were the same as those for the second key secondary endpoint (BOR of CR or CRi with an MRD-negative bone marrow based on all manufacturing facilities) (see below).
- 82.0% (95% CI: 68.6, 91.4; p<0.0001) of patients achieved a BOR of CR or CRi per IRC assessment with an MRD-negative bone marrow within 3 months of tisagenlecleucel infusion

1.3.2 Final analysis of ORR in patients treated with US-manufactured product – Study B2202

Among the 88 patients enrolled, 68 were administered tisagenlecleucel: 63 patients with US-manufactured product and 5 with EU-manufactured product. None of the 5 patients who received tisagenlecleucel manufactured from the EU facility had follow-up of ≥ 3 months and thus these patients did not contribute to the ORR analysis presented (N=63).

Among the 68 patients who received tisagenlecleucel, the median time from infusion to the data cut-off date of 23-Nov-2016 was 8.76 months (range: 0.3 to 18.5) in this analysis.

Results remain consistent with those previously reported for the interim analysis when the initial 50 patients had completed 3 months of follow-up (Table 1-2):

- The ORR per IRC assessment was 82.5% (95% CI: 70.9, 90.9) within 3 months of the infusion: 63.5% of patients achieved a BOR of CR and 19.0% attained CRi
  - No discrepancies were noted between the Investigator and IRC assessments of the primary endpoint

Robustness of the primary analysis of ORR was further confirmed by the results of a series of predefined sensitivity analyses, with ORRs ranging from 65.8% to 84.2% across different analysis sets (with the lower bounds of all 95% CIs exceeding 20%). A homogeneous treatment effect was evident across all subgroups.

Secondary endpoints

Clinical benefit of tisagenlecleucel was further supported by:

- Consistently high remission rates with long DoRs in Study B2202 and the supportive trials (Studies B2101J and B2205J), with the respective median DoRs yet to be reached (Table 1-2)
- Relapse-free rates at Month 6 of 75.4% (95% CI: 57.2, 86.7) in Study B2202, and 73.4% (95% CI: 57.7, 84.1) and 66.4% (95% CI: 39.3, 83.6), respectively, in Studies B2101J and B2205J
- Responses typically occurring rapidly (within the initial 28 days post-tisagenlecleucel infusion) and bone marrow MRD data confirming the depth and quality of these remissions, with all patients with CR or CRi also achieving MRD-negative status
- Data from Study B2101J, where with a longer follow-up, the estimated probability of survival was 80.6% at 1 year and 62.6% at 2 years post-tisagenlecleucel infusion (with a maximum follow-up of 40.5 months)
- Estimated probabilities of survival of 88.6% at Month 6 and 79.2% at Month 12 in Study B2202, with corresponding figures of 75.7% at Month 6 and 61.7% at Month 12 in Study B2205J

Table 1-2 Overview of key efficacy endpoints – Studies B2101J, B2205J, and B2202

	Supportive trials		Pivotal trial
	Study B2101J N=55	Study B2205J N=29	Study B2202 [1] N=63
ORR within 3 months			
ORR (CR plus CRi) – n (%)	52 (94.5)	20 (69.0)	52 (82.5)
95% confidence interval	84.9, 98.9	49.2, 84.7	70.9, 90.9
p-value	N/A	<0.0001	<0.0001 [2]
CR	38 (69.1)	18 (62.1)	40 (63.5)
CRi	14 (25.5)	2 (6.9)	12 (19.0)
NR	3 (5.5)	7 (24.1)	5 (7.9)
Unknown	0	2 (6.9)	6 (9.5)
Response with MRD-negative bone marrow			
ORR with MRD-negative bone marrow – n (%)	49 (89.1)	18 (62.1)	52 (82.5)
95% confidence interval	77.8, 95.9	42.3, 79.3	70.9, 90.9
p-value	N/A	N/A	<0.0001 [2]

	Supportive trials		Pivotal trial
	Study B2101J	Study B2205J	Study B2202 [1]
	N=55	N=29	N=63
Duration of remission			
Events/responders (%)	16/52 (30.8)	8/20 (40.0)	11/52 (21.2)
Median DoR (mo)	NR	NR	NR
95% confidence interval			7.5, NE
KM estimate of remission at Month 6 (%)	73.4	66.4	75.4
95% confidence interval	57.7, 84.1	39.3, 83.6	57.2, 86.7
Event-free survival			**N=68 (FAS)**
Events/all patients (%)	19/55 (34.5)	17/29 (58.6)	20/68 (29.4)
Median EFS (mo)	NR	6.9	NR
95% confidence interval		1.5, NE	7.1, NE
KM estimate of EFS at Month 6 (%)	74.6	55.0	70.2
95% confidence interval	60.2, 84.5	35.3, 70.9	55.1, 81.1
Overall survival			**N=68 (FAS)**
Events/all patients (%)	15/55 (27.3)	10/29 (34.5)	11/68 (16.2)
Median OS (mo)	32.7	NR	16.6
95% confidence interval	21.0, NE		16.6, NE
KM estimate of OS at Month 6 (%)	85.1	75.7	88.6
95% confidence interval	72.4, 92.3	55.7, 87.6	77.4, 94.4

CR Complete remission; CRi Complete remission with incomplete blood count recovery; DoR Duration of remission; EFS Event-free survival; FAS Full Analysis Set; KM Kaplan-Meier; MRD Minimal residual disease; N/A Not applicable; NE Not estimable; NR Not reached; ORR Overall remission rate; OS Overall survival

[1] Results correspond to the final analysis of ORR in patients treated with US-manufactured product. Sixty-eight patients received tisagenlecleucel, 5 of whom received EU-manufactured product; this final analysis was therefore based on the 63 patients who received US-manufactured product.

[2] No formal significance testing was conducted as this endpoint was met at the interim analysis. The nominal p-value is presented.

1.4 Safety of tisagenlecleucel in B-cell ALL

The safety profile of tisagenlecleucel is well characterized and toxicity is manageable at appropriately-trained sites, although some patients require intensive care unit (ICU)-level care. Safety in the global pivotal Study B2202 was consistent with the tisagenlecleucel safety profile reported previously in the single-center B2101J trial and multicenter Study B2205J in pediatric and young adult patients with r/r B-cell ALL.

As Studies B2202 and B2205J had near-identical study designs and enrolled similar patient populations, data (N=97) from these 2 multicenter trials were combined to form the focus for the sections that follow. This facilitates a more robust safety assessment in a larger pool of patients and provides a longer duration of follow-up.

Patients in this Safety Pool experienced a broad range of adverse events (AEs) even prior to treatment with lymphodepleting chemotherapy or tisagenlecleucel infusion. Adverse events were consistent with those expected in patients receiving chemotherapy for r/r B-cell ALL. These events were manageable per the relevant product information. Among the 94 patients who received lymphodepleting chemotherapy, 79.8% reported ≥ 1 AE; grade 3 and 4 AEs were reported in 11.7% and 27.7% of patients, respectively. As expected for patients undergoing

lymphodepleting chemotherapy, the most commonly reported events were white blood cell (WBC) count decreased (12.8%, primarily grade 4), nausea (11.7%), anemia (10.6%), pyrexia (10.6%), neutrophil count decreased (8.5%, mostly grade 4), and febrile neutropenia (7.4%, all grade 3).

- Tisagenlecleucel is administered as a single infusion and the majority of AEs, serious adverse events (SAEs), and adverse events of special interest (AESIs) occur within the initial 8-week period post-infusion (Table 1-3):
  - SAEs occurred in 72.2% of patients in the initial 8 weeks compared with 23.8% in the period between 8 weeks and 1 year

Table 1-3 Overview of grade 3/4 AEs and SAEs post-tisagenlecleucel infusion by time period – Studies B2202 and B2205J

	Initial 8-week period N=97 n (%)		8 weeks to 1 year N=80 n (%)	
Grade 3/4 adverse event (AE)	80	(82.5)	33	(41.3)
Suspected to be related	70	(72.2)	15	(18.8)
Serious adverse event (SAE)	70	(72.2)	19	(23.8)
Suspected to be related	67	(69.1)	3	(3.8)

The most prevalent AEs are listed in Table 1-4 while the most important clinical events (all AESIs) are summarized below:

- Cytokine-release syndrome (CRS), a class effect and expected on-target toxicity related to the mechanism of action, is the most frequent event associated with tisagenlecleucel (reported in 81.4% of patients, and as grade 3/4 in 44.3%). Of note, all events occurred within the initial 6 weeks post-infusion. Clinical and laboratory measures ranged from mild CRS (constitutional symptoms and/or grade 2 organ toxicity) to severe CRS (grade ≥ 3 organ toxicity, aggressive clinical intervention, and/or potentially life-threatening). The degree of CRS severity correlated with disease burden, early onset of CRS, and the early onset of fever.
  - The median duration of CRS was 8 days
  - 44.3% of patients were admitted to the ICU for the treatment of CRS, where the median duration of the ICU stay was 8 days
  - Cytokine-release syndrome was effectively managed with a well-tested (and protocol-mandated) treatment algorithm that included supportive care and, when indicated, administration of anti-interleukin (IL)-6 cytokine-directed therapy with tocilizumab (and subsequently siltuximab if unresolved) and a clinically-based CRS grading scale. Anti-cytokine therapy was administered to 34.0% of patients resulting in CRS improvement or resolution. Supportive care included vasopressor use in 26.8% of patients and ventilatory support in 16.5%. Dialysis was initiated in 11.3% of patients, mostly for the control of fluid overload. No fatalities have been attributed to refractory CRS in any of the pediatric and young adult r/r B-cell ALL studies to date.
- Neurological toxicities (defined as events in the non-infectious encephalopathy/delirium standard MedDRA query [SMQ]) included aphasia, tremor, seizures, confusion, and encephalopathy and were reported in 40.2% of patients within the initial 8-week period

post-tisagenlecleucel infusion; 11.3% of patients experienced grade 3 events but no grade 4 events were reported (see Table 6-16). Such self-limited neurological events in the context of concurrent CRS are a known class effect of T cell directed cellular or T cell engager immunotherapies. Elevated cytokine levels may be partly responsible for these neurological events, although direct CAR T-cell toxicity on the central nervous system (CNS) is possible but has not been demonstrated. These events are transient and typically resolve without intervention or require modest supportive care.
Of note, no cases of cerebral edema were reported.

- Other AESIs (including tumor lysis syndrome [TLS], cytopenias unresolved by Day 28, febrile neutropenia, and infections) and B-cell aplasia are also well characterized and are manageable with supportive care
  - CAR T-cell therapy can potentially lead to TLS; however, with the use of prophylaxis as described in the studies, only a limited number of patients (3.1%) developed TLS post-tisagenlecleucel infusion
  - Persistent grade 3 and grade 4 cytopenias (reported as an AE in 13.4% and 16.5% of patients, respectively) were observed beyond Day 28 post-tisagenlecleucel infusion. Prolonged neutropenia (based on laboratory reporting) was associated with grade 3/4 infections in 8.1% of patients. Cytopenias are generally manageable with standard clinical measures. Two fatalities (one due to a systemic fungal infection and one attributed to encephalitis [human herpes virus-6 (HHV-6)]) occurred where prolonged neutropenia (both pre- and post-infusion) was considered to have played a contributory role.
  - Febrile neutropenia, an expected AE in patients receiving lymphodepleting chemotherapy and tisagenlecleucel, was reported in 36.1% of patients within the initial 8-week period post-infusion. When assessed by the presence of fever (body temperature >38.3°C within ±1 day) in conjunction with grade 3/4 neutropenia, this occurred in 60.8% of patients.
  - Prolonged B-cell aplasia is an on-target effect and was seen in all patients with remission and is treated with immunoglobulin replacement therapy
- No lentiviral vector associated AEs were observed. No generation of replication-competent lentivirus (RCL) was detected and no insertional oncogenesis has been observed post-tisagenlecleucel infusion.
- Twenty-one deaths were reported in Studies B2202 and B2205J (the Safety Pool) post-tisagenlecleucel infusion
  - 2 of 4 deaths within the initial 30-day period post-infusion were attributed to disease progression. The remaining 2 deaths were due to cerebral hemorrhage in the setting of disseminated intravascular coagulation (DIC) and embolic stroke from an intracardiac mucormycotic mass (see Table 6-10 for brief case narratives).
  - 14 of the 17 deaths >30 days post-infusion were attributed to disease progression. The remaining 3 patients died secondary to infection; respective causes were determined to be encephalitis, systemic mycosis, and bacterial lower respiratory tract infection (see Table 6-10 for brief case narratives).

Table 1-4 Adverse events post-tisagenlecleucel infusion occurring in at least 20% of patients at any time by grade and time period – Studies B2202 and B2205J

	Initial 8-week period N=97			8 weeks to 1 year N=80			All patients N=97		
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Patients with at least 1 AE	**95 (97.9)**	**23 (23.7)**	**57 (58.8)**	**66 (82.5)**	**19 (23.8)**	**14 (17.5)**	**97(100.0)**	**22 (22.7)**	**60 (61.9)**
Non-hematologic AEs									
Cytokine release syndrome	79 (81.4)	19 (19.6)	24 (24.7)	0	0	0	79 (81.4)	19 (19.6)	24 (24.7)
Pyrexia	32 (33.0)	8 (8.2)	3 (3.1)	11 (13.8)	2 (2.5)	0	40 (41.2)	10 (10.3)	3 (3.1)
Decreased appetite	32 (33.0)	19 (19.6)	1 (1.0)	6 (7.5)	0	0	38 (39.2)	19 (19.6)	1 (1.0)
Vomiting	31 (32.0)	3 (3.1)	0	7 (8.8)	2 (2.5)	0	33 (34.0)	4 (4.1)	0
Headache	29 (29.9)	2 (2.1)	0	9 (11.3)	0	0	32 (33.0)	2 (2.1)	0
Hypotension	30 (30.9)	10 (10.3)	13 (13.4)	2 (2.5)	1 (1.3)	1 (1.3)	31 (32.0)	10 (10.3)	14 (14.4)
Nausea	26 (26.8)	5 (5.2)	0	9 (11.3)	2 (2.5)	0	31 (32.0)	7 (7.2)	0
AST increased	30 (30.9)	11 (11.3)	7 (7.2)	3 (3.8)	2 (2.5)	0	30 (30.9)	11 (11.3)	7 (7.2)
ALT increased	28 (28.9)	12 (12.4)	0	5 (6.3)	4 (5.0)	0	29 (29.9)	14 (14.4)	0
Diarrhoea	23 (23.7)	1 (1.0)	0	8 (10.0)	1 (1.3)	0	29 (29.9)	2 (2.1)	0
Hypokalaemia	26 (26.8)	11 (11.3)	2 (2.1)	2 (2.5)	1 (1.3)	1 (1.3)	27 (27.8)	11 (11.3)	3 (3.1)
Tachycardia	25 (25.8)	4 (4.1)	1 (1.0)	2 (2.5)	0	0	25 (25.8)	4 (4.1)	1 (1.0)
Fatigue	19 (19.6)	1 (1.0)	0	6 (7.5)	0	0	24 (24.7)	1 (1.0)	0
Hypoxia	21 (21.6)	9 (9.3)	7 (7.2)	2 (2.5)	2 (2.5)	0	23 (23.7)	11 (11.3)	7 (7.2)
Hypophosphataemia	20 (20.6)	10 (10.3)	1 (1.0)	1 (1.3)	1 (1.3)	0	21 (21.6)	11 (11.3)	1 (1.0)
Cough	13 (13.4)	0	0	10 (12.5)	0	0	20 (20.6)	0	0

	Initial 8-week period N=97			8 weeks to 1 year N=80			All patients N=97		
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Hematologic AEs									
Febrile neutropenia	35 (36.1)	33 (34.0)	2 (2.1)	3 (3.8)	3 (3.8)	0	35 (36.1)	33 (34.0)	2 (2.1)
Hypogammaglobulinaemia	22 (22.7)	3 (3.1)	0	13 (16.3)	1 (1.3)	0	33 (34.0)	4 (4.1)	0
Anaemia	31 (32.0)	14 (14.4)	1 (1.0)	4 (5.0)	2 (2.5)	0	32 (33.0)	15 (15.5)	1 (1.0)
WBC count decreased	29 (29.9)	5 (5.2)	17 (17.5)	8 (10.0)	2 (2.5)	1 (1.3)	30 (30.9)	5 (5.2)	17 (17.5)
Neutrophil count decreased	24 (24.7)	2 (2.1)	19 (19.6)	12 (15.0)	4 (5.0)	5 (6.3)	28 (28.9)	4 (4.1)	21 (21.6)
Platelet count decreased	25 (25.8)	4 (4.1)	13 (13.4)	5 (6.3)	1 (1.3)	1 (1.3)	27 (27.8)	5 (5.2)	13 (13.4)
Lymphocyte count decreased	18 (8.6)	11 (11.3)	5 (5.2)	4 (5.0)	2 (2.5)	0	20 (20.6)	13 (13.4)	5 (5.2)

AE Adverse event; ALT Alanine aminotransferase; AST Aspartate aminotransferase; WBC White blood cell

Health-related quality-of-life (HRQoL) data provided insight into the benefit-risk profile from a patient perspective enabling an evaluation as to whether the observed efficacy benefit was achieved at the expense of deterioration in QoL. Questionnaires were completed at scheduled visits by patients aged ≥ 8 years prior to the patient interacting with the Investigator or undergoing any clinical assessments. The majority of patients who failed to respond to treatment and those who relapsed dropped out from the study and as a result their patient-reported outcome (PRO) data were unavailable. Results therefore correspond to patients who were responding to treatment.

- Improvements in patient-reported outcomes were observed at 3 and 6 months in Study B2202
  - Mean changes from baseline in the pediatric quality of life inventory (PedsQL) questionnaire score were 5.4 at Day 28 (n=32), 13.5 at Month 3 (n=30), and 15.3 at Month 6 (n=25), with a 4.4-point change reflecting the minimal clinically important difference (Varni et al 2003)
  - Mean changes from baseline in the EuroQol visual analogue scale (EQ VAS) questionnaire score were 5.0 at Day 28 (n=32), 14.1 at Month 3 (n=28), and 15.5 at Month 6 (n=24), with estimated minimally important differences in the range from 7 to 10 among cancer patients (Pickard et al 2007)

In conclusion, the safety profile of tisagenlecleucel is well characterized and toxicity is manageable in the hands of appropriately-trained healthcare providers, although patients may require ICU-level care for the management of severe CRS. Safety was consistent across the 3 clinical studies conducted in pediatric and young adult patients with r/r B-cell ALL.

1.5 Benefit-risk assessment for tisagenlecleucel in B-cell ALL

Current multi-agent regimens serve the majority of first-line patients with ALL well with cure rates exceeding 85% (Hunger and Mullighan 2015); however, approximately 15% of pediatric and young adult patients with ALL will relapse. Relapsed ALL is recognized as one of the leading causes of cancer death in pediatric and young adult patients (Tallen et al 2010). Although most pediatric patients with relapsed ALL will achieve a second remission, the challenge remains to maintain this remission as most patients who relapse once will subsequently relapse again and ultimately succumb to their disease (Ko et al 2010, Tallen et al 2010, Martin et al 2012).

The limited treatment options available for pediatric and young adult patients with relapsed or refractory disease fail to address the needs of this population (Table 1-5). Innovative treatment strategies based on the use of novel anti-leukemia agents are therefore urgently needed. Allogeneic SCT is a potentially curative option but eligibility is dependent upon both disease and patient characteristics and treatment is associated with significant morbidity and mortality. Tisagenlecleucel represents the first salvage therapy in this setting that may be curative and be administered as a definitive therapy as opposed to a bridge to allo-SCT.

Compelling efficacy of tisagenlecleucel in pediatric and young adult patients with r/r B-cell ALL was demonstrated in the pivotal registration Study B2202 and two supportive trials, with high ORRs (with high rates of MRD-negative status achieved for patients in remission) and long DoRs (Table 1-5), without further therapy in the majority of patients.

Table 1-5 Efficacy overview: comparison with available treatments for pediatric and young adult patients with r/r B-cell ALL

	Clofarabine monotherapy	Blinatumomab	Tisagenlecleucel		
	Jeha et al 2006	von Stackelberg et al 2016 [1]	B2101J	B2205J	B2202
No. of patients	61	70	55	29	68
Prior SCT	29.5%	57.1%	63.6%	58.6%	56.5%
≥ 3 prior regimens	62.3%	11.4%	89.1%	NA [2]	60.3%
ORR (CR plus CRi)	19.7%	38.6%	94.5%	69.0%	82.5% [3]
Median OS	**3.0 mo**	**7.5 mo**	**32.7 mo [4]**	**NR**	**16.6 mo [5]**
12-month OS	20%	38%	80.6%	61.7%	79.2%
Early mortality (≤ 30 days)	24.6%	7.1%	5.5%	6.8%	2.9%

CR Complete remission; CRi Complete remission with incomplete blood count recovery; NR Not reached; ORR Overall remission rate; OS Overall survival; SCT Stem-cell transplantation

[1] Based on all 70 patients who received the recommended dose in Phase-I or -II studies
[2] Median prior of lines of therapy: 3 (range: 1-9)
[3] Based on the 63 patients in the Efficacy Analysis Set
[4] Survival probability beyond 24 months should be interpreted with caution as only 11 patients had follow-up >24 months
[5] Median value should be interpreted with caution as approximately 84% of patients were still alive (and therefore censored in the analysis) at the time of the data cut-off, and only 2 patients were at risk at timepoints beyond 16 months

Safety of tisagenlecleucel is predictable and toxicity is manageable by appropriately-trained healthcare providers. Treatment is associated with significant toxicity in the initial 8 weeks post-tisagenlecleucel infusion, especially in patients with high disease burden; however, AEs can be managed with the application of specific algorithms/guidelines at centers with appropriate training in tisagenlecleucel safety management (see Table 6-14 for an example). Furthermore, a return to near-normal QoL was observed (for patients in remission) in the pivotal trial along with a reduction in the incidences of SAEs and grade 3/4 AEs after 8 weeks. A Risk Evaluation and Mitigation Strategy (REMS) is proposed – the goal of which is to educate healthcare providers (HCPs) about the serious risks of CRS and neurological events.

- The majority of patients develop CRS (with the severity correlating with disease burden). This can be effectively managed with a detailed treatment algorithm that was established in the 3 trials forming this program. Key elements of this algorithm include an improved CRS grading scale and the administration of anti-cytokine therapy. Cytokine release syndrome is limited to the first 6 weeks post-infusion. No fatal cases of refractory CRS have been observed in pediatric and young adult patients with B-cell ALL to date.
- Neurological events (defined as events in the non-infectious encephalopathy/delirium SMQ) are transient, tend to be associated with CRS, and typically occur within the initial 30 days post-tisagenlecleucel infusion
- Other AEs are well characterized and are manageable with supportive care
- Patients with pre-existing and prolonged neutropenia post-tisagenlecleucel infusion may be at increased risk for severe or fatal infections
- Five deaths were reported in Studies B2202 and B2205J post-tisagenlecleucel infusion that were not attributed to the underlying disease (these deaths were due to cerebral

hemorrhage in the setting of DIC, embolic stroke from an intracardiac mucormycotic mass, and 3 deaths secondary to infection)

In conclusion, tisagenlecleucel offers pediatric and young adult patients with r/r B-cell ALL a clinically important benefit with high remission rates, long DoRs, and improved survival rates without additional therapy. These results compare favorably to the poor outcomes reported with other current treatment modalities. The safety profile of tisagenlecleucel is manageable when administered by appropriately-trained site personnel although patients may require ICU-level care for the management of severe CRS. Overall, tisagenlecleucel is associated with a positive benefit-risk profile and represents a new treatment paradigm for these patients with high unmet medical need.

2 Background information

2.1 Epidemiology and outcome

Acute lymphoblastic leukemia is the most common malignancy among children in the US. Approximately 5000 cases of B-cell ALL are diagnosed annually, with 60% of these cases occurring in patients under the age of 20 years (Hunger and Mullighan 2015).

Current multi-agent regimens result in cure rates exceeding 85% (Hunger and Mullighan 2015).

Approximately 15% of children and young adults with ALL will relapse, with long-term survival rates after first relapse of 40% to 50% (Reismüller et al 2013). Relapsed ALL remains one of the leading causes of cancer death in children (Raetz et al 2008, Parker et al 2010, Pui et al 2011).

Patients with ALL who relapse after allo-SCT also have a poor prognosis.

Although primary induction failure is rare at presentation, occurring in only 2% to 3% of patients, refractory ALL also remains a therapeutic challenge (Ceppi et al 2016).

2.2 Current treatment options for r/r B-cell ALL

2.2.1 Relapsed/refractory ALL

Current treatment options for pediatric and young adult patients with r/r B-cell ALL include:

- Re-induction chemotherapy to obtain remission
- Definitive post-induction therapy
  - Chemotherapy alone for patients with off-therapy relapse and good MRD response to induction
  - Chemotherapy to obtain MRD-negative status and subsequent allo-SCT in patients with
    - Early relapse
    - Late relapse and MRD-positive status post-induction
    - Second or later relapses
  - Targeted therapies
  - Other experimental agents
- Supportive care with non-curative palliative goals

2.2.2 Outcomes for patients with r/r B-cell ALL

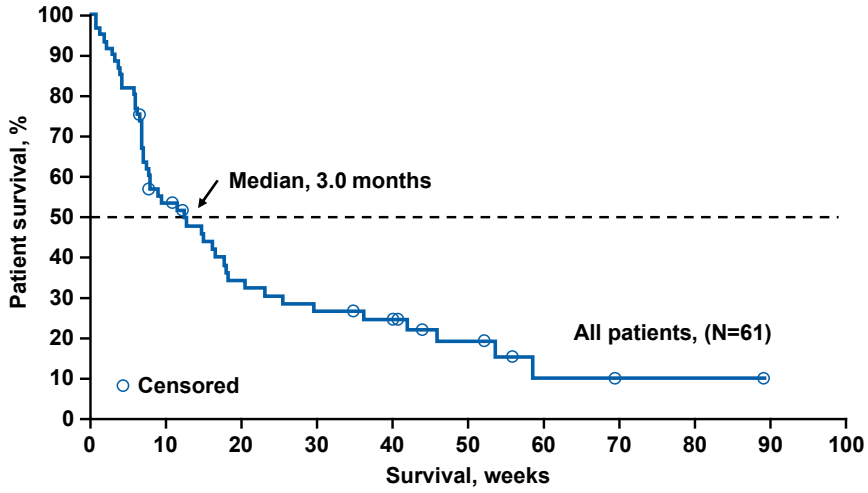
Limitations of the available treatment options include:

- Standard chemotherapy and SCT are associated with limited efficacy:
  - 5-year leukemia-free survival rates of 30%, 34%, and 22% for children in first, second, and third CR, respectively (Klingebiel et al 2010)
  - 12-month OS rates of approximately 79%, 61%, and 43%, respectively, for children in first, second, and third CR at the time of SCT (Bondarenko et al 2016)

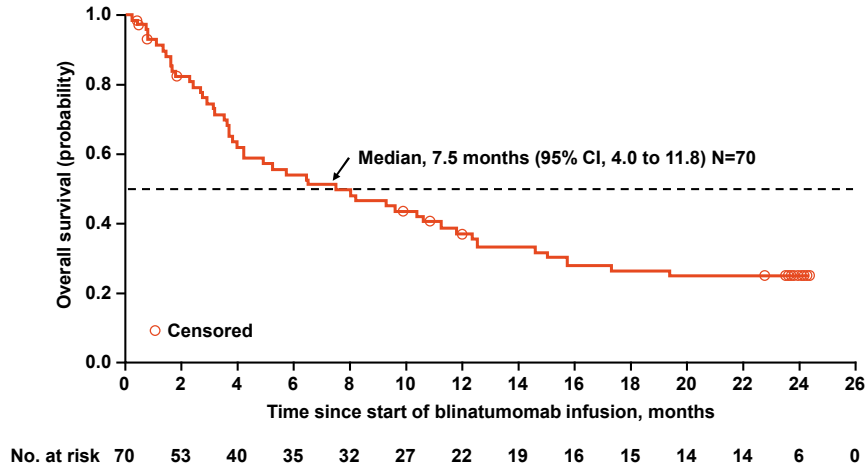
- New chemotherapeutic agents have not resulted in an improvement in survival (Figure 2-1 and Table 2-1) and are used primarily as a bridge to SCT
  - Salvage chemotherapy with clofarabine is associated with poor outcomes (20% CR and a median OS of 20% to 30% at 12 months when administered either as a single agent or in combination) and high levels of toxicity (including febrile neutropenia, infections, anorexia, hypotension, and nausea) (Jeha et al 2006)
- Bispecific T cell engager therapies also provide only a modest improvement (Figure 2-1)
  - Blinatumomab was approved based on a 32.9% CR and a median OS of 7.5 months. Serious adverse events (including febrile neutropenia, pyrexia, and pneumonia) were reported in 65% of patients (von Stackelberg et al 2016).
- Patients who are eligible for a second SCT represent a small minority and survival for this group is approximately 10% to 15%

Figure 2-1 Current outcomes for pediatric patients with r/r ALL

Clofarabine monotherapy: Phase-II trial in pediatric r/r ALL (N=61)



Blinatumomab: Phase-I/II trial in pediatric r/r ALL (N=70)



ALL Acute lymphoblastic leukemia; CI Confidence interval; r/r Relapsed/refractory

Table 2-1 Efficacy of available treatments for pediatric and young adult patients with r/r B-cell ALL

	Clofarabine monotherapy	Blinatumomab	
	Jeha et al 2006	von Stackelberg et al 2016	
	Phase II	Phase II	Phase I/II combined [1]
No. of patients	61	44	70
Prior SCT	29.5%	56.8%	57.1%
≥ 3 prior regimens	62.3%	6.8%	11.4%
ORR (CR plus CRi)	19.7%	31.8%	38.6%
Median OS	**3.0 months**	**NA**	**7.5 months**
12-month OS	20%	NA	38%
Early mortality (≤ 30 days)	24.6%	NA	7.1%

CR Complete remission; CRi Complete remission with incomplete blood count recovery; NA Not available; ORR Overall remission rate; OS Overall survival; SCT Stem-cell transplantation

[1] Based on all 70 patients who received the recommended dose in Phase-I or -II studies

Significant unmet medical need in r/r B-cell ALL

Despite current treatment options, approximately 620 pediatric and young adult patients with B-cell ALL experience relapse each year in the US (Maude et al 2015). Treatment options for these patients are limited and are associated with poor outcomes and high toxicity. Many patients with r/r B-cell ALL remain incurable.

As a result, there is an unmet medical need for novel treatment options for pediatric and young adult patients with r/r B-cell ALL to provide:

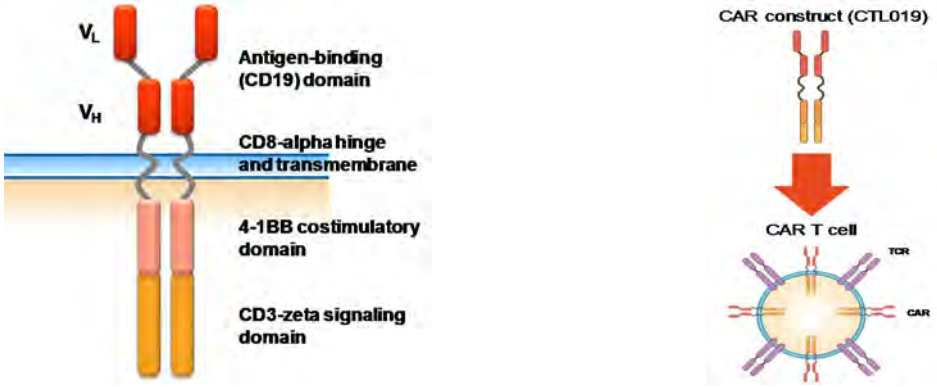
- Deep (MRD-negative) and durable remission
- Prolonged survival (with curative treatment opportunities)
- Improved QoL

2.3 Rationale for the development of tisagenlecleucel in B-cell ALL

2.3.1 Mechanism of action

Tisagenlecleucel is an autologous, immunocellular cancer therapy which involves reprogramming a patient's own T cells with a transgene encoding a CAR to identify and eliminate CD19-expressing malignant and non-malignant cells. The CAR is comprised of a murine single-chain antibody fragment which recognizes CD19 and is fused to intracellular signaling domains from 4-1BB (CD137) and CD3-zeta (Figure 2-2). The CD3-zeta component is critical for initiating T-cell activation and anti-tumor activity while 4-1BB enhances the expansion and, importantly, the persistence of tisagenlecleucel. Upon binding to CD19-expressing cells, the CAR transmits a signal to promote T-cell expansion, activation, target cell elimination, and persistence of tisagenlecleucel. The transduced T cells expand in vivo to engage and eliminate CD19-expressing cells and may exhibit immunological endurance to help support long-lasting remission (Maude et al 2014, Porter et al 2015, Turtle et al 2016).

Figure 2-2 Tisagenlecleucel construct and mechanism of action

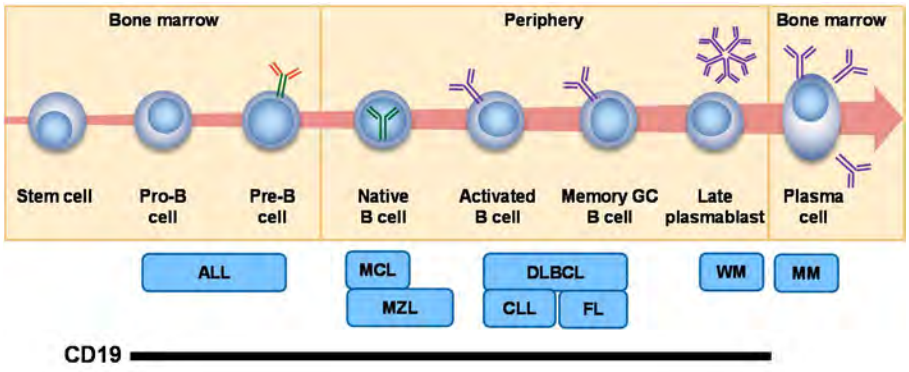


The CAR construct enters the T cell via lentiviral vector transduction
Binding to CD19-expressing target cells transduces a signal to the T cells to promote T cell expansion, activation, target cell killing, and persistence of tisagenlecleucel

Tisagenlecleucel expands in vivo, engages and eliminates CD19 expressing cells, and may exhibit immunological persistence that results in long-lasting remission.

- As a cell surface antigen, CD19 is expressed throughout most stages of normal B-cell differentiation (early pre-B to mature B cells) and is rarely lost during the process of neoplastic transformation. It is present on a wide range of B-lymphoid malignancies that span different stages of B-cell differentiation, including pre-B ALL, mantle-cell lymphoma (MCL), marginal zone lymphoma (MZL), diffuse large B-cell lymphoma (DLBCL), chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), and Waldenström's macroglobulinemia (WM) (Scheuermann and Racila 1995) (Figure 2-3).

Figure 2-3 CD19 as target for CAR T cell therapy in treating B-cell malignancies



ALL Acute lymphoblastic leukemia; CLL Chronic lymphocytic leukemia; DLBCL Diffuse large B-cell lymphoma; FL Follicular lymphoma; MCL Mantle-cell lymphoma; MM Multiple myeloma; MZL Marginal zone lymphoma; WM Waldenström's macroglobulinemia

- CD19 is not expressed on hematopoietic stem cells or other hematopoietic lineages; tisagenlecleucel activity is therefore limited to the B cell lineage
- A murine xenograft model of primary B-cell ALL was used to demonstrate CD19-mediated T cell expansion, persistence, and antitumor activity of tisagenlecleucel (Milone et al 2009). A murine syngeneic model was used to identify the anticipated on-target depletion of CD19+ normal B cells (Kochenderfer et al 2010). More recently, preclinical

in vivo models for CLL (Fraietta et al 2016) and MCL (Ruella et al 2016) have been developed wherein tisagenlecleucel clearly demonstrates CD19-mediated T cell expansion and anti-tumor activity, further supporting the potential activity of tisagenlecleucel in these CD19+ B-cell malignancies.

2.4 Manufacturing process

Tisagenlecleucel is an autologous immunocellular therapy that utilizes the patient's own cells as the starting material. The manufacturing process is designed to generate a highly pure T cell population. Full product quality release testing is completed prior to release of the product. The batch-to-batch consistency of the manufacturing process was confirmed with regards to appearance, identity, purity, quantity, potency, and safety properties of tisagenlecleucel (see Table 2-2).

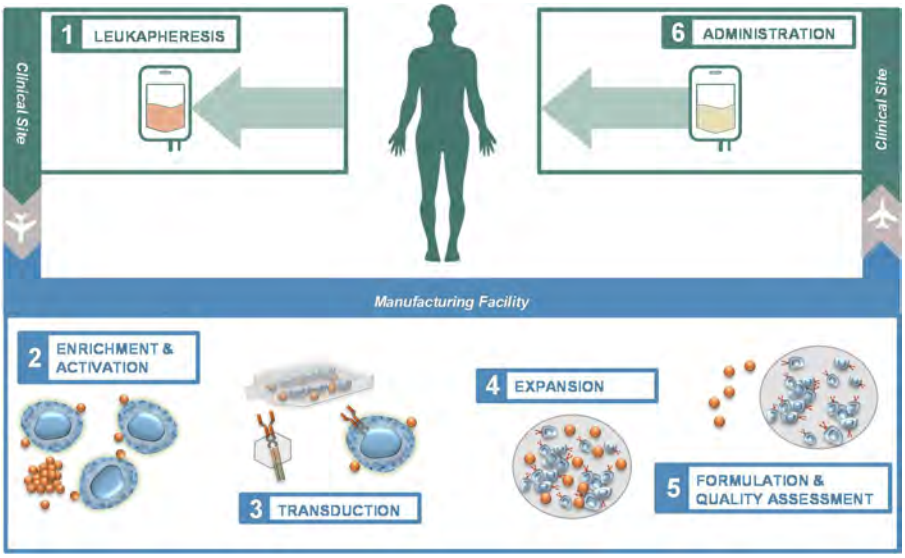
Key steps in the manufacturing process

Key steps in the tisagenlecleucel manufacturing process can be summarized as follows (Figure 2-4):

- Patients undergo leukapheresis to collect their blood mononuclear cells; these are cryopreserved and shipped to the manufacturing facility using a dedicated courier service (and stored at ≤ -120°C)
  - Each leukapheresis is assigned to a dedicated team who only work on a single product at a time (see chain of identity in Section 2.4.3)
- After thawing, cells undergo a procedure to remove cells detrimental to CAR transduction and growth (i.e. monocytes and B-lineage lymphoblasts) and to enrich for T cells
- T cells are activated ex vivo with anti-CD3/CD28 antibody-coated beads and transduced with a self-inactivating minimal lentiviral vector containing the anti-CD19 CAR transgene
- Transduced T cells are subsequently expanded ex vivo and then washed, formulated, and cryopreserved
- Full release testing is completed prior to release of the cryopreserved final product. Cells are then shipped to the clinical site.

Patients undergo bridging chemotherapy as needed to control their leukemia while the transduced T cells are being manufactured and subsequently receive lymphocyte-depleting chemotherapy immediately prior to tisagenlecleucel infusion.

Figure 2-4 Manufacturing process: tisagenlecleucel is an autologous immunocellular therapy



Further details of the manufacturing process

The tisagenlecleucel manufacturing process is continuous without any intermediates or drug substance holding steps.

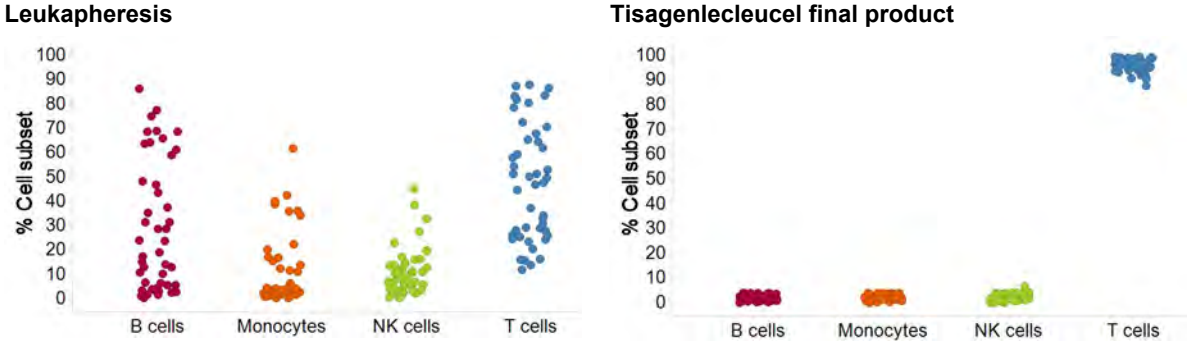
Batches and scale definition

A tisagenlecleucel batch is produced for each patient from one leukapheresis material batch.

Multiple patient batches can be manufactured at the same time as the manufacturing of each batch uses dedicated equipment, materials, and personnel (see chain of identity in Section 2.4.3).

Due to the inherent variability of the cellular composition of the patient's leukapheresis material, the tisagenlecleucel manufacturing process includes unit operations to remove undesired cells (primarily monocytes and B-lineage cells). The enrichment and selective expansion of T cells results in a highly pure T-cell population as shown in Figure 2-5 for the full range of patient starting material.

Figure 2-5 Manufacturing experience: consistent T-cell product from variable patient material – Study B2202



Culture conditions effectively support T cell growth despite the diversity in the individual growth properties for any given patient.

Process description summary

Step 2. Enrichment and activation

At Day 0, T cell enrichment is performed based on the cellular composition of the patient leukapheresis material. Percentage of monocytes and percentage of B lineage cells are measured by flow cytometry. The percentage of monocytes and B lineage cells dictates the choice of pathway for T cell enrichment.

The stimulation of T cells is performed using immunomagnetic beads bearing anti-CD3/CD28 monoclonal antibodies, Dynabeads® CD3/CD28 Cell Therapy Systems (CTS)™.

The cell-bead suspension then undergoes magnetic separation, retaining the bead-bound $CD3^+/CD45^+$ T cell fraction.

Step 3. Transduction

The bead-bound cells in this positive fraction are advanced to lentiviral vector transduction. Lentiviral vector transduction utilizes a self-inactivating minimal lentiviral vector that encodes the CD19-targeting CAR; transduction is performed twice, over 2 successive days. (Note: vector is produced by a third-party provider.)

Step 4. Expansion

On Day 3, following the second incubation period, the cell culture is washed to remove non-integrated vector and residual vector particles. The washed cells are seeded into a disposable culture system. The culture is continued over a period of several days until the cell number is sufficient to enable harvest.

Step 5. Formulation

When the cell count reaches the required minimum number of total viable cells, the cells are separated from the beads using a magnetic separation device, harvested, and washed.

The cells are formulated in the cryoformulation medium based on the cell count for each patient dose.

The individual patient dose is distributed into individual cryobags and vials. The final product is then placed into a precooled controlled rate freezer, for cryopreservation.

Cryopreserved tisagenlecleucel bags are subsequently stored in the vapor-phase of liquid nitrogen in monitored liquid nitrogen storage tanks, in a secure, limited access area until final release and shipping (a 9-month shelf-life has been proposed).

The final dose for pediatric patients with ALL is set based on the individual's body weight:

- For patients weighing ≤ 50 kg, the final product will be formulated at a dose of 0.2–5.0×10^6 transduced viable T cells/kg body weight as a single dose infusion
- For patients weighing >50 kg, the final product will be formulated at a dose of 0.1–2.5×10^8 transduced viable T cells as a single dose infusion

2.4.1 Controlling key tisagenlecleucel product attributes (step 5 - quality assessment)

Specific processes are in place to maintain the safety, purity, identity, and potency of each patient-specific tisagenlecleucel product (Table 2-2); further details of the specifications are not disclosed here as this information is considered to be proprietary (note: this information was shared with FDA as part of the BLA).

- Safety and purity testing confirms the absence of any contaminants and impurities in the product
- Identity ensures the presence of the CAR transgene
- Potency testing ensures that there is appropriate CAR expression and cytokine secretion
  - The biological effect of the expressed genetic sequence (CAR-19) is tested at the tisagenlecleucel final product by measuring interferon (IFN)-γ release per transduced cell in response to CD19 expressing target cells.
    Although differences in IFN-γ release per transduced cell are observed between individual patient batches, a consistent mean IFN-γ release per transduced cell is observed between the vector batches used to manufacture tisagenlecleucel to date. The variability observed between different tisagenlecleucel product batches is attributed to variable cell starting material quality and patient variability.

Table 2-2 Quality assurance of tisagenlecleucel

Appearance and description	**Impurities**
Color	Determination of residual beds by microscopy
Identity	Percentage of viable CD19+ B cells
Identity by CAR qPCR	**Quantity**
Safety	Total cell count
Bacterial endotoxins	Number of viable cells (calculated)
Sterility	Dose (calculated)
Mycoplasma	**Potency**
Determination of VSV-G DNA by qPCR	Determination of CAR expression by flow cytometry
Purity	Release of IFN-γ in response to CD19-expressing target cells
Percentage of viable T cells	
Determination of transduction efficiency by CAR qPCR	
Cell viability	

CAR Chimeric antigen receptor; IFN Interferon; qPCR Quantitative polymerase chain reaction; VSV-G Vesicular stomatitis virus-G

2.4.2 Lentiviral vector

Considerable care was taken in the selection, design, testing, and monitoring of the vector and vector-transduced cells. Of particular concern were the potential for the genetic insertion to lead to secondary cancer and/or the ability of the vector elements to recombine to produce a pathogenic virus. To address these concerns, a self-inactivating minimal lentiviral vector was selected to offer an improved safety profile relative to gamma retroviruses while still allowing for stable, long-term expression of the transgene in T cells. The vector was also designed to minimize the risk of recombination events (to prevent the generation of RCL) and oncogenicity.

To assure an appropriate safety profile of the lentiviral vector, various studies were performed including an integration study which showed no evidence for preferential integration near genes of concern or preferential outgrowth of genetically modified cells harboring integration sites of concern.

The lentiviral vector used in tisagenlecleucel manufacture is manufactured using single-use disposable consumables to Good Manufacturing Practices (GMP), using a well characterized and robust manufacturing process, and supported by a wide range of testing to ensure quality attributes are maintained.

The tisagenlecleucel lentiviral vector raw material has been demonstrated to robustly and predictably lead to the transduction of patient T cells with the CD19-targeting CAR, thereby conferring the ability to target and kill CD19+ leukemia cells on the patient cells.

Vector and product testing has shown no RCL events to date and there has been no evidence of insertional oncogenesis.

2.4.3 Chain of identity

Tisagenlecleucel is a personalized immunocellular therapy, precisely engineered and manufactured in a patient-centric, quality-controlled continuous process with a rigorous chain of identity:

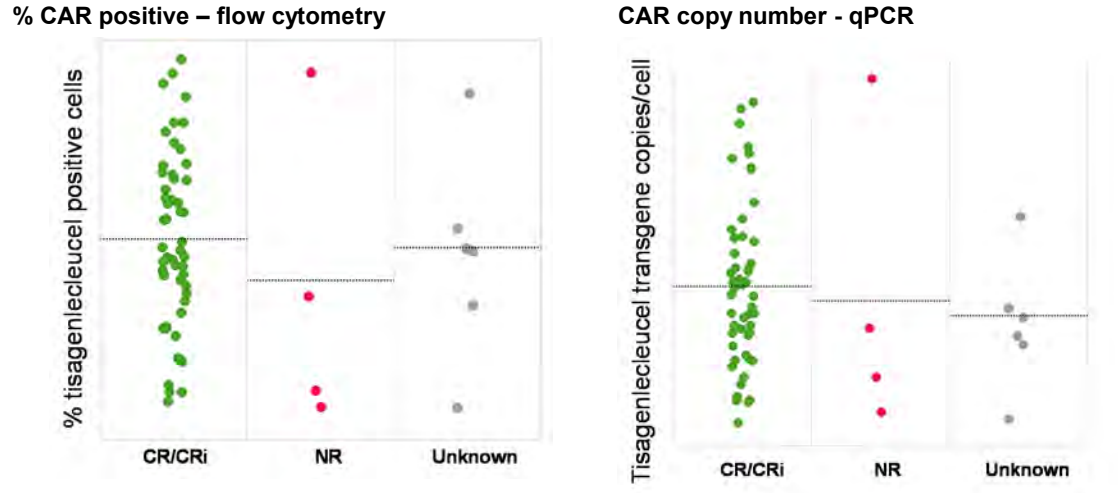
- Meticulous quality and safety controls are implemented across all steps in the manufacturing process
- All product-contacting consumables used throughout the process are single-use, disposable consumables
- Novartis has established a chain of identity system controlled by a validated Good X Practice (GxP) IT solution (consistent with the use of standard blood banking labeling)
- Novartis uses well-established, existing chain of identity standards (including Foundation for the Accreditation of Cellular Therapy [FACT]-accredited procedures and International Society of Blood Transfusion [ISBT]-128 labeling standards) which seamlessly integrate with the Novartis GxP system to maintain a rigorous chain of identity from leukapheresis through manufacturing to patient infusion
- Four key identifiers – name, date of birth, donor identification number (DIN) (or apheresis ID), and the single unique identifier, the batch ID, are linked together throughout this process.
    - A dedicated team is assigned to work on a single product at a time (with no transfer between teams)

2.4.4 Correlation between characteristics of engineered product and clinical outcomes

Two key aspects of the cell product, CAR transduction and in vitro product potency, and their correlation to clinical outcomes are summarized in this section. These measures show the quantity and activity of both the transgene and the cells, and are representative of the full set of product attributes determined during the pivotal trial.

No correlation was observed between transduction efficiency or transgene copy number and BOR at 3 months (Figure 2-6), with positive patient outcomes across the range of transgene positive cells and copy numbers.

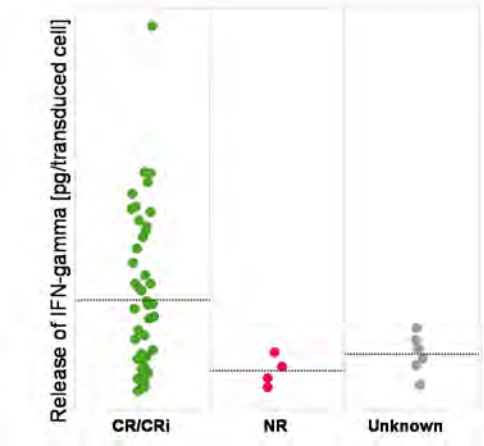
Figure 2-6 Best overall response vs CAR transduction – Study B2202



CAR Chimeric antigen receptor; CR Complete remission; CRi Complete remission with incomplete blood count recovery; NR Non-responder; qPCR Quantitative polymerase chain reaction

Positive patient outcomes were also observed across the complete range of acceptable potency assay results although there were more non-responding patients at the lower end of potency (Figure 2-7).

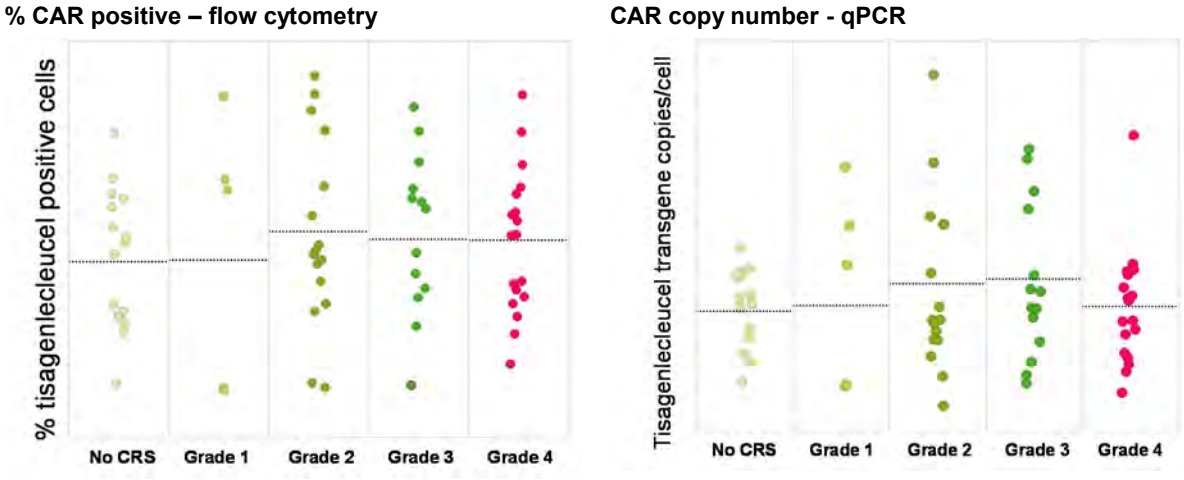
Figure 2-7 Best overall response vs product in vitro potency – Study B2202



CR Complete remission; CRi Complete remission with incomplete blood count recovery; IFN Interferon; NR Non-responder

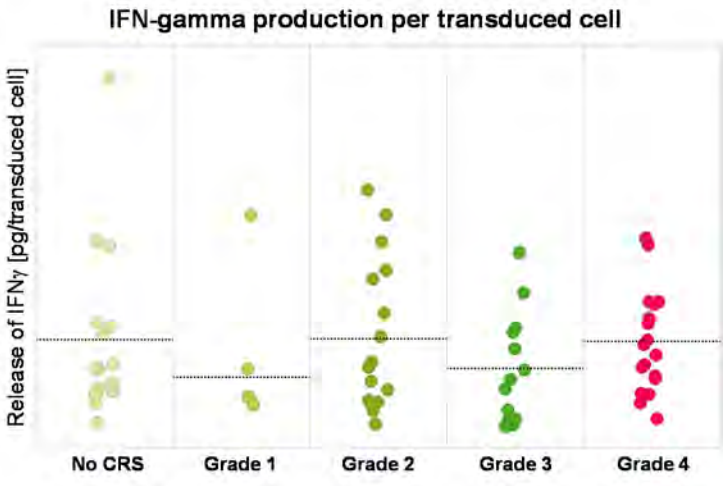
Product characteristics were also evaluated against CRS. The severity of CRS did not correlate with transduction efficiency or transgene copy number (Figure 2-8) and no correlation was observed between IFN-γ secretion and CRS grade (Figure 2-9).

Figure 2-8 Cytokine release syndrome vs CAR transduction – Study B2202



CAR Chimeric antigen receptor; CRS Cytokine release syndrome; qPCR Quantitative polymerase chain reaction

Figure 2-9 Cytokine release syndrome vs product in vitro potency – Study B2202



CRS Cytokine release syndrome; IFN Interferon

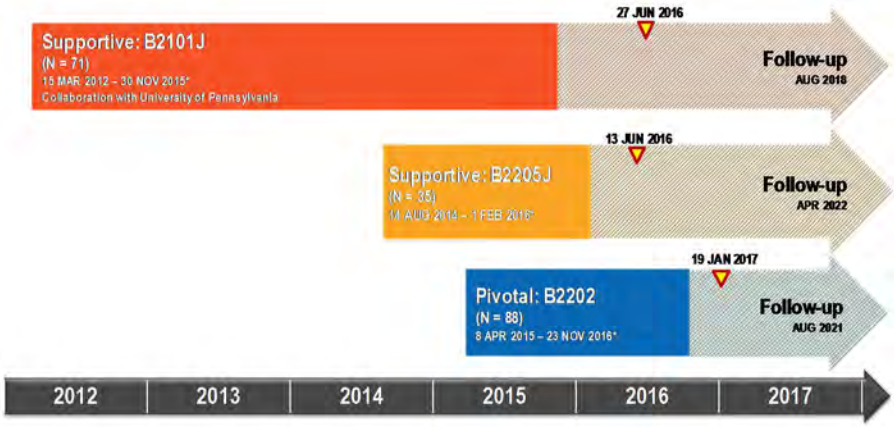
In summary, Novartis has gained extensive experience in manufacturing CAR-T cells.

- The manufacturing process is highly reproducible and results in a high-quality cell product
- Patient responses are seen across the full range of acceptable product quality attributes

2.5 Clinical development program

The efficacy and safety of tisagenlecleucel have been evaluated in 3 trials involving over 150 pediatric and young adult patients with r/r B-cell ALL (Table 1-1 and Figure 2-10).

Figure 2-10 Overview of tisagenlecleucel BLA in pediatric and young adult patients with r/r B-cell ALL



ALL Acute lymphoblastic leukemia; BLA Biologics License Application; r/r Relapsed/refractory

* Dates provided reflect first patient first visit to the data cut-off date for the primary analysis

▽ Database lock for primary analysis.

The database lock for the primary analysis of Study B2202 was 01-Nov-2016 (conducted after the first 50 patients infused with tisagenlecleucel had either completed 3 months of follow-up or had discontinued for any reason); at this timepoint, the primary and key secondary endpoints were met. A subsequent update of these data (corresponding to when the initial 50 patients were followed-up for ≥ 6 months or had discontinued for any reason) had a database lock date of 19-Jan-2017.

- **Study B2101J** is a single-arm, open-label, single-center, Phase-I/IIa trial (enrolled: N=71; infused: N=55), conducted at the Children's Hospital of Philadelphia, with the objective of assessing the long-term persistence, in vivo proliferation, anti-tumor activity, and safety of tisagenlecleucel in patients with r/r and incurable CD19+ B-cell malignancies (CD19+ leukemia or lymphoma). This was the first clinical study to be conducted using this novel cellular immunotherapy in this patient population. Entry criteria were designed to include pediatric and young adult patients aged 1 to 24 years with CD19+ B-cell malignancies with no available curative treatment options (such as autologous or allo-SCT) who had a limited prognosis (several months to <2-year survival) with currently available therapies. Up to three infusions and a wide dose range were allowed.
- **Study B2205J** is a single-arm, open-label, multicenter, Phase-II trial (enrolled: N=35; infused: N=29) conducted in the US, and similar both in design and study objectives to the pivotal registration trial (Study B2202). Due to the earlier start date, there is a longer duration of follow-up available for this trial relative to Study B2202. Other differences from Study B2202 include a smaller number of enrolled patients (35 vs. 88 patients, respectively), and the geographical location of the clinical and manufacturing sites.
- **Study B2202** is the pivotal registration trial and is an international, multicenter, single-arm, open-label Phase-II trial designed to evaluate the efficacy and safety of tisagenlecleucel in pediatric and young adult patients with r/r B-cell ALL (enrolled: N=88; infused: N=68). Patients were aged between 3 years at the time of screening and 21 years at the time of initial diagnosis. The single-arm study design was supported by the absence of effective therapies in this setting, and the high unmet medical need of the target patient population.

Tisagenlecleucel manufacturing process and manufacturing sites

The initial encouraging data for the efficacy of tisagenlecleucel were from Studies B2101J and B2205J where the product was first manufactured using the Penn manufacturing process (manufactured at the Cell and Vaccine Production Facility at Penn). Subsequent collaboration between Penn and Novartis led to the transfer of this process to the Novartis facility in Morris Plains, NJ. The manufacturing process (for both the US and ex-US) and analytical testing were further developed to deliver a consistent process in terms of product quality, as determined by testing for appearance, identity, purity, quantity, potency, and safety of the product.

- In Study B2205J, tisagenlecleucel batches were manufactured for 26 patients at the Cell and Vaccine Production Facility at Penn, and for 3 patients at the Novartis Morris Plains manufacturing facility using the Penn manufacturing process and release specifications. Of note, a site-to-site product comparability exercise was performed between the two manufacturing sites; batches were similar in terms of cell product release, functional response to CD19-expressing target cells, in-process data, and cellular composition.
- All tisagenlecleucel batches in Study B2202 were manufactured at the Novartis Morris Plains manufacturing facility with the exception of 5 patient batches produced at the Fraunhofer-Institut für Zelltherapie und Immunologie, Leipzig, Germany. The source of lentiviral vector was consistent for all tisagenlecleucel batches.

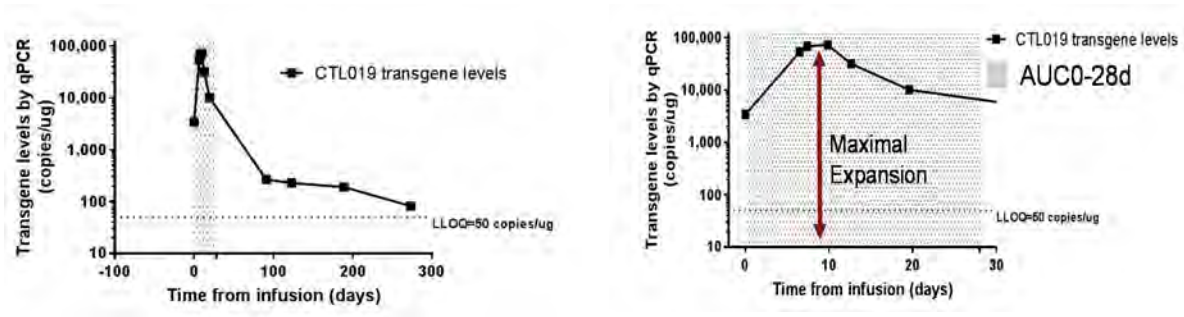
3 Clinical pharmacology

3.1 Cellular kinetics: general characteristics

Levels of tisagenlecleucel transgene (copies/µg genomic DNA) were monitored in peripheral blood and bone marrow using quantitative polymerase chain reaction (qPCR) and/or flow cytometry. Derived parameters of interest included Cmax, AUC0-28d (where Day 28 was the date for the initial assessment of clinical response), and AUC0-84d reflecting expansion of the modified T cells following infusion of tisagenlecleucel. Tlast and Clast, the time of last measureable transgene and the level of transgene at that time-point respectively, reflect persistence of the transgene in the body. Representative cellular kinetic profiles determined by qPCR presenting transgene levels over time are depicted in Figure 2-10 for a single patient in which a CR or CRi was observed.

Figure 3-1 Cellular kinetic profile: representative data from a single patient

Full profile **Expansion during the initial 28 days**



LLOQ Lower limit of quantification; qPCR Quantitative polymerase chain reaction

Units for the y-axis are transgene copies/µg of genomic DNA (with an input of 200 ng of DNA)

3.1.1 Cellular kinetics in peripheral blood

Primary conclusions drawn from the analysis of cellular kinetic data were consistent across the 3 trials (Studies B2202, B2205J, and B2101J):

- Cmax and AUC0-28d in peripheral blood were higher in patients attaining CR or CRi (responders) (by 104% and 73.5%, respectively) than in patients with no response (NR) in Studies B2202 and B2205J
- Median Tmax for the transgene in patients with CR or CRi was 10 days; this compared to a delayed Tmax of 20 days in patients with NR
- Tisagenlecleucel was measurable up to 380 days (Tlast) in patients with CR or CRi (median: 102 days) and for up to 83.9 days in patients with NR (median: 27.8 days) in Studies B2202 and B2205J (where the period of assessment was shorter). The CD19-CAR transgene was measurable up to 780 days in Study B2101J (median Tlast: 196 days).
- The geometric mean half-life (T1/2) in patients with CR or CRi was 20 days (percentage coefficient of variation [CV%]: 319.7%) and 2 days (CV%: 47.0%) in patients with NR, respectively, in Study B2101J
- Results based on a flow cytometry assay were in agreement with those based on qPCR

Mean or median peripheral transgene AUC0-28d, Cmax, and Tlast were higher for patients with CR or CRi (responders) compared to non-responders (NRs), although the number of non-responders was low (Table 3-1).

Table 3-1 Comparison of peripheral blood transgene cellular kinetic parameters in responders vs. non-responders – pooled data from Studies B2202 and B2205J

Parameter	Statistics	Responder N=62		Non-responder N=8	
AUC0-28d (copies/µg DNA ×days)	n	61		6	
	Geo-mean (CV%)	318,000	(177.8)	156,000	(99.4)
Cmax (copies/µg)	n	61		7	
	Geo-mean (CV%)	55,700	(155.4)	20,000	(71.6)
Tlast	n	62		8	
	Median (min, max)	102	(17.8, 380)	27.8	(20.9, 83.9)

AUC0-28d Exposure or levels of transgene attained during the initial 28 days following infusion of tisagenlecleucel; Cmax Maximum (peak) expansion of transgene post-tisagenlecleucel infusion; CV Coefficient of variation; Responder Patient with CR or CRi; Tlast Time of last observed quantifiable transgene

3.1.2 Cellular kinetics in bone marrow aspirates

Transgene levels in the bone marrow of patients with CR or CRi were highest at Day 28 followed by a subsequent decline, and were measureable up to 6 months. The shape of the profile was consistent in both the bone marrow and peripheral blood. Bone marrow collections post-Day 28 were unavailable for the majority of non-responding patients as these patients came off study. Transgene levels in bone marrow aspirates were on average 44% of the transgene level in peripheral blood on Day 28 (and 67% and 69%, respectively, at 3 and 6 months).

3.1.3 Factors influencing cellular kinetics

Intrinsic factors including baseline cytogenetics and disease characteristics, race, body weight, gender, and disease status did not impact cellular kinetic parameters (AUC0-28d and Cmax). Patients with higher tumor burden at enrollment had higher expansion as determined by AUC0-28d and Cmax. High tumor burden (defined as maximum morphologic blast count and MRD in bone marrow of $\geq 50\%$) immediately prior to tisagenlecleucel infusion in Study B2101J was associated with increased expansion:

- AUC0-28d, AUC0-84d, and Cmax increased by approximately 243%, 273%, and 144%, respectively, relative to patients with low tumor burden

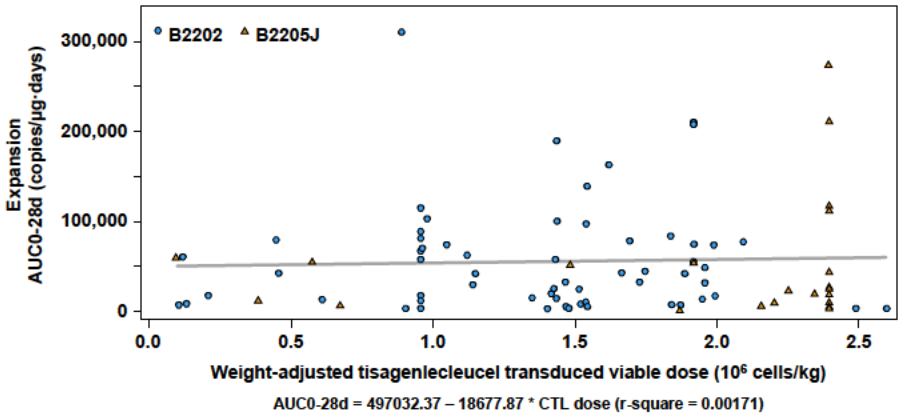
Extrinsic factors, including the number of lines of prior therapy and prior allo-SCT and the administration of anti-cytokines (tocilizumab and corticosteroids), had no impact on expansion and persistence.

3.2 Dose-cellular kinetics

Patients received a range of doses in Study B2202, with an attempt to administer the highest feasible dose; however, due to patient-specific characteristics, this was not always possible resulting in a wide range of doses being tested.

No apparent relationship was evident between dose (both total and body weight-adjusted) and cellular kinetic parameters (Cmax and AUC0-28d [Figure 3-2]), as r-square values were <0.1. Therefore, dose does not correlate with expansion (AUC0-28d).

Figure 3-2 Dose-cellular kinetic analysis: relationship between AUC0-28d and dose – Studies B2202 and B2205J



AUC0-28d Exposure or levels of transgene attained during the initial 28 days following infusion of tisagenlecleucel

Results of dose-response analyses are summarized in Section 5.3.

3.3 Relationship between manufacturing release characteristics and cellular kinetics

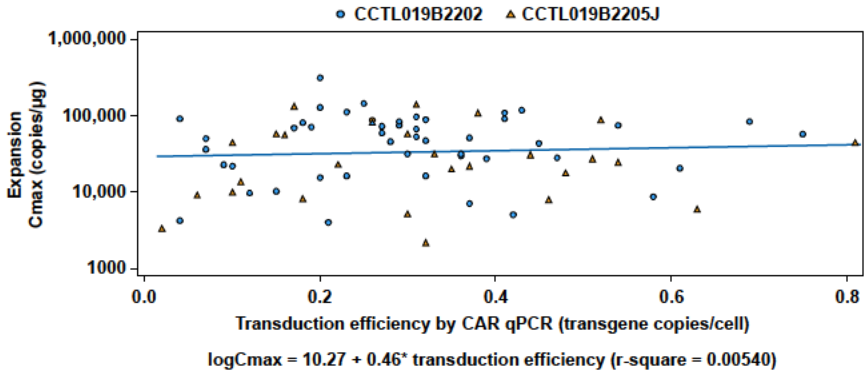
Appropriate analytical methods (e.g. flow and qPCR) were developed to capture the expansion and persistence of tisagenlecleucel.

No relevant differences in cell exposure metrics (as determined in Studies B2202 and B2205J) were observed between products manufactured at Penn and Morris Plains.

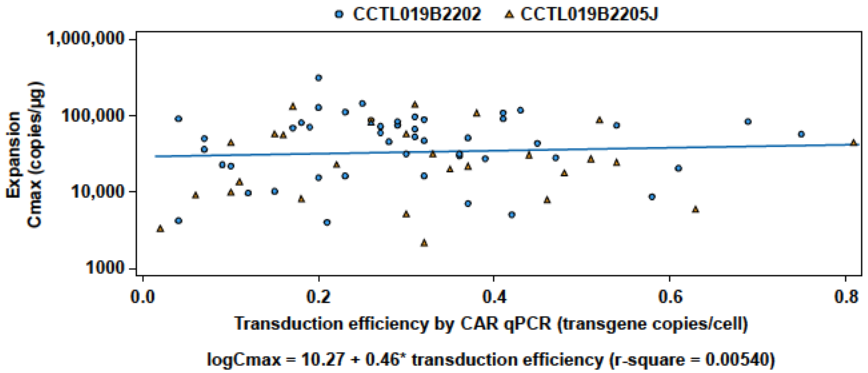
No significant relationship was observed between the manufacturing release characteristics (percent T cells, transduction efficiency, cell viability, and total cell count; referred to as product attributes) and cellular kinetic parameters of tisagenlecleucel (Figure 3-3).

Figure 3-3 Relationship between manufacturing release characteristics and cellular kinetic parameters – Study B2202 or Studies B2202 and B2205J

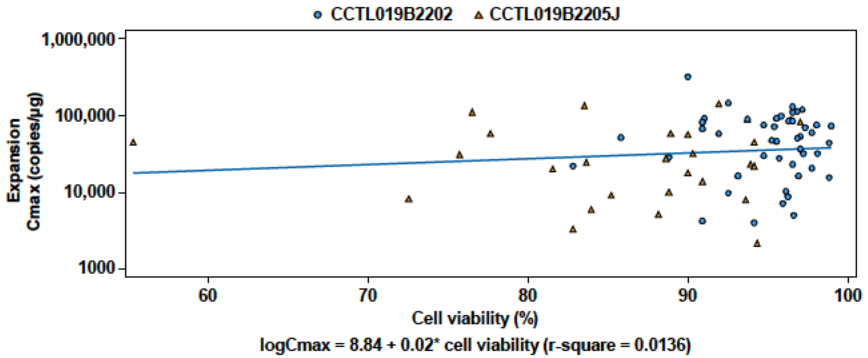
Transduction efficiency by qPCR



Transduction efficiency by flow cytometry



Cell viability



CAR Chimeric antigen receptor; Cmax Maximum (peak) expansion of transgene post-tisagenlecleucel infusion; qPCR Quantitative polymerase chain reaction

4 Key aspects of the clinical development program

4.1 Regulatory consultations

The US FDA was consulted on the design of the pediatric and young adult r/r ALL program, including the proposed design of the pivotal Study B2202. The FDA evaluated the protocol for Study B2202 and agreement was reached in terms of:

- A single-arm trial was considered to be acceptable, because the study investigated the efficacy and safety in a population with a high unmet medical need, with clofarabine as a precedent, and salvage therapy or palliative treatment as the only available treatment option
- Preliminary results of Study B2102J showed high remission rates and promising preliminary safety data
- The initial proposed dose range was appropriate
- The proposed statistical methodology was prespecified and deemed to be appropriate
- Entry criteria served to enroll a clinically identifiable population of pediatric and young adult patients with r/r B-cell ALL
- Choice of the primary endpoint of ORR (CR and CRi) was considered to be appropriate. The primary analysis was to be conducted once 50 patients were infused and had completed ≥ 3 months follow-up or had discontinued for any reason.

Breakthrough therapy designation was initially granted on 07-Jul-2014 under the Penn Investigational New Drug (IND) and subsequently regranted on 07-Apr-2016 under the Novartis IND for r/r B-cell ALL. An early filing strategy was proposed and agreed to by FDA at a Pre-BLA Meeting.

4.2 Dose-selection rationale

No formal dose-escalation studies were conducted. The dose used in Phase II was based on experience gained from earlier studies (from Study B2101J [phase-I pediatric ALL] and Studies B2102J and A2201 [adult CLL]) (Table 4-1). Of particular note, remissions were observed across all doses administered in these prior trials and preliminary safety was established in pediatric and young adult patients with ALL and adult patients with CLL.

Table 4-1 Justification for proposed dose range

Cellular kinetics	Efficacy	Safety
Dose and in vivo expansion are independent across wide range of doses and expansion (multi-log)	Remissions observed across entire dose range studied Remission rate similar across dose quartiles No apparent effect of dose on EFS categories Probability of remission at lowest doses tested carries favorable benefit-risk	No impact of dose on CRS (grade 3/4) No impact of dose on neurotoxicity or cytopenias

CRS Cytokine release syndrome; EFS Event-free survival

Treatment is a single intravenous infusion, and the protocol-specified dose range was based on patient weight, with patients ≤ 50 kg receiving weight-based dosing and those >50 kg receiving a fixed dose:

- Patients ≤ 50 kg: 0.2 to 5.0×10^6 transduced viable T cells/kg
- Patients >50 kg: 0.1 to 2.5×10^8 transduced viable T cells

This wide dose range was deemed acceptable because no clear relationship was apparent between in vivo expansion (Cmax and AUC0-28d) and tisagenlecleucel dose (see Section 3.2).

4.3 General methodological considerations

4.3.1 Trial design and conduct

Clinical trials evaluating CAR T therapies typically consist of a screening phase (leukapheresis), a pre-treatment phase (enrollment, lymphodepleting chemotherapy), and a treatment phase. Patients undergo a waiting period during which the cell product is prepared before it can be released and administered to the patient.

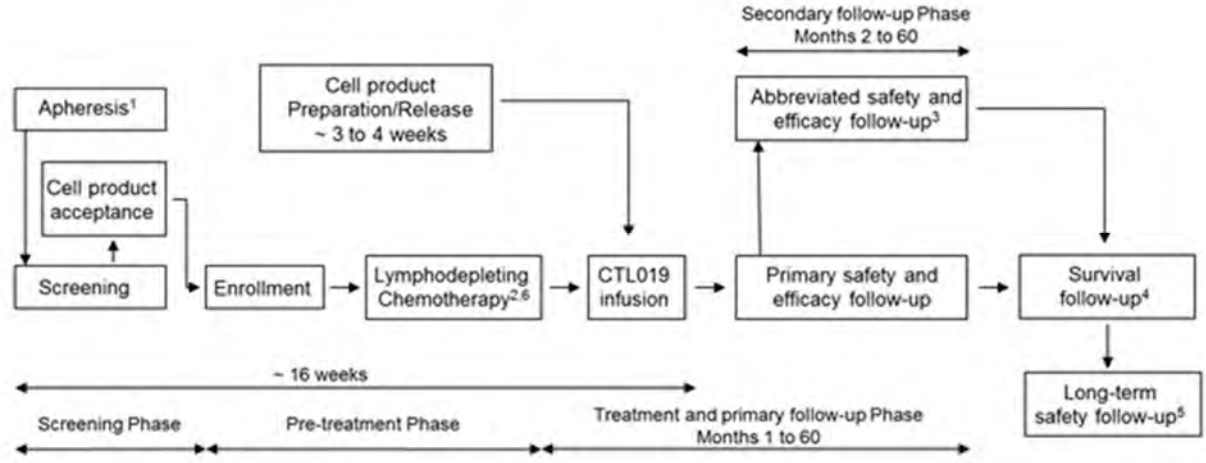
- Patients receiving tisagenlecleucel are thoroughly evaluated and closely monitored both prior to and post-infusion to minimize the risk of potential AEs
- Prior to tisagenlecleucel infusion, patients receive lymphodepleting chemotherapy (see Section 6.2.1)
- The tisagenlecleucel product is released for infusion once all required safety and quality release criteria have been met
- Patients receive tisagenlecleucel as a single infusion without the need for repeat dosing
- To lessen the side effects associated with T cell infusion (fever, chills and/or nausea), patients receive pre-medication with acetaminophen or paracetamol and diphenhydramine or an H_1 anti-histamine. Patients also receive standard supportive care for immunosuppressed/chemotherapy-treated patients, including infection management.

Evidence of clinical efficacy was based primarily on the pivotal single-arm global multicenter Phase-II Study B2202 (Table 1-1). All patients had CD19-positive B-cell ALL with morphologic marrow tumor involvement at registration (≥ 5% lymphoblasts), and had disease that was chemorefractory, relapsed after allo-SCT, or were otherwise ineligible for allo-SCT. Study B2202 was designed to evaluate benefit in pediatric and young adult patients with r/r B-cell ALL with a high unmet medical need.

Studies B2202 and B2205J had near-identical study designs, and enrolled similar patient populations (Figure 4-1 and Table 4-2). The choice of the single-arm study design was appropriate and was supported by the absence of effective standard-of-care therapies in this setting, coupled with the high unmet medical need of the target patient population. Furthermore, compelling data from Study B2101J were already available in terms of high CR rates and durable remissions; this posed ethical challenges to conducting randomized trials in the absence of adequate comparator treatments (Maude et al 2014).

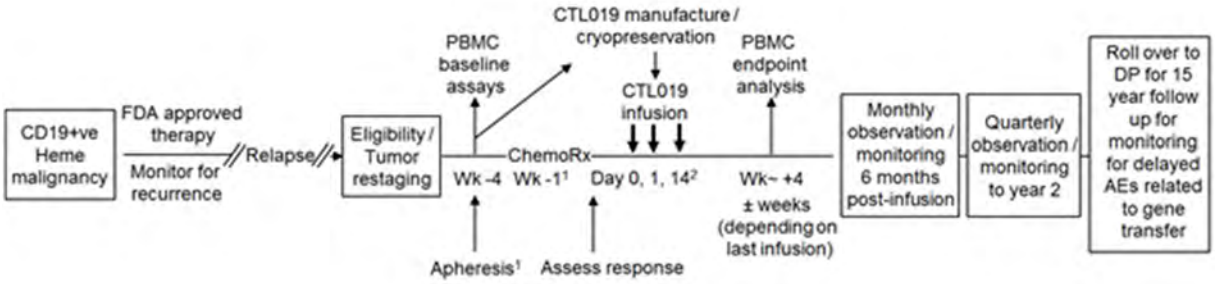
Differences in the design of Study B2101J relative to the other two studies are summarized in Figure 4-2 and Table 4-2.

Figure 4-1 Trial design – Studies B2202 and B2205J



[1] Performed prior to study entry
[2] As indicated per protocol
[3] Only for patients who dropped out of the primary follow-up before Month 60
[4] Patients were to be followed for survival until the end of the trial, or until they were enrolled in the long-term follow-up
[5] Long-term safety follow-up conducted per Health Authority guidance under a separate protocol
[6] To be completed 2 to 14 days prior to tisagenlecleucel infusion

Figure 4-2 Trial design – Study B2101J



DP Destination protocol; FDA Food and Drug Administration; PBMC Peripheral blood mononuclear cells
[1] If required
[2] Day 14 is tentative based on response to prior infusions

Table 4-2 Trial design comparisons

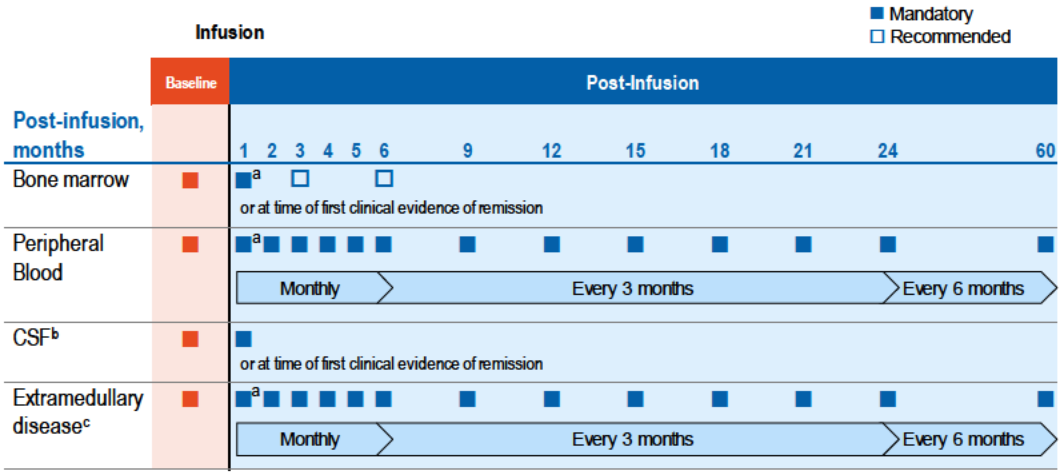
Studies B2202 and B2205J	Study B2101J
Number of sites: Multicenter (B2202: 25 sites; B2205J: 9 sites)	Single center
Tisagenlecleucel dose range: Single infusion with narrower dose range (see Table 1-1)	Multiple infusions (10%, 30%, 60%) allowed with broader total dose range (see Table 1-1)

Studies B2202 and B2205J	Study B2101J
Population:	
More narrowly defined patient population - similar across the two studies: - Active bone marrow disease (≥ 5% blasts) at enrollment - No prior anti-CD19 therapy - No CNS3 disease - Aged 3 years at time of Screening to 21 years at time of initial diagnosis	Broader patient population: - Morphologic CR patients allowed (both MRD-positive and negative) - Prior anti-CD19 therapy allowed - Non-CNS3 and CNS3 disease - Aged 1 year at time of Screening to 24 years at time of initial diagnosis
Lymphodepleting chemotherapy:	
Choice of: - Fludarabine and cyclophosphamide (preferred) - Cytarabine and etoposide	Multiple choices depending on the patient's underlying disease and prior therapies. Fludarabine and cyclophosphamide were the agents of choice.
IRC assessment:	
Yes	No
Response confirmation:	
Required	Not required
Manufacturing process and manufacturing site:	
B2202: Novartis manufacturing process – manufactured at the Morris Plains, NJ (US) facility with the exception of 5 patients (produced at the Fraunhofer-Institut für Zelltherapie und Immunologie, Leipzig, Germany) Single source of vector used for this trial B2205J: Penn manufacturing process – manufactured at the Cell and Vaccine Production Facility of Penn with the exception of 3 patients (produced at the Morris Plains, NJ facility but using the Penn manufacturing process and release specifications)	Penn manufacturing process – manufactured at the Cell and Vaccine Production Facility of Penn
Manufacturing pretesting:	
No requirement for manufacturing test expansion	Positive manufacturing test expansion required for the majority of the study
Safety reporting prior to tisagenlecleucel infusion:	
Adverse events reported per modified safety reporting criteria	Adverse events reported only when leading to discontinuation
CRS reporting:	
Changing of CRS toxicity grades reported as separate AEs with corresponding start/end dates in order to characterize the evolvement of the CRS	Each CRS event as single event with maximum toxicity grade during the entire period reported
Cytopenia during the 28-day period post-tisagenlecleucel infusion:	
Cytopenia reported as AE if clinically significant per Investigator	Cytopenia only reported as AE in the clinical database beginning 28 days after infusion

AE Adverse event; CNS Central nervous system; Non-CNS3 ALL Active CNS involvement excluded; CR Complete remission; CRS Cytokine release syndrome; IRC Independent Review Committee; US United States

Scheduling of efficacy assessments is summarized in Figure 4-3.

Figure 4-3 Efficacy assessment schedule – Study B2202



CNS Central nervous system; CSF Cerebrospinal fluid; CT Computed tomography; MRI Magnetic resonance imaging

[a] Confirmed 4 weeks after initial assessment
[b] CNS imaging (CT/MRI) was conducted as clinically indicated
[c] Via physical examination, including assessment of CNS symptoms

4.3.2 Efficacy endpoints and statistical methodology

The efficacy analyses performed in Studies B2202 and B2205J were robust, consistent between studies, and appropriate to assess the clinical benefit of tisagenlecleucel in pediatric and young adult patients with r/r B-cell ALL. Tumor responses were assessed by an IRC in both studies. Tumor response assessments were based on Novartis Guidelines for Response Assessment in ALL (Table 4-4), which in turn are based on the National Comprehensive Cancer Network Guidelines for ALL (NCCN Version 1.2013). Response assessments in Study B2101J were performed in accordance with the standard practice at the site.

Overall remission rate (CR plus CRi) as determined by an IRC was the primary endpoint in Studies B2202 and B2205J (Table 4-3). The choice of ORR as the primary endpoint was based on:

- ORR being a widely accepted standard outcome measurement in ALL (Appelbaum et al 2007)
- The established correlation of ORR with long-term outcome (Cheson et al 2003, Appelbaum et al 2007)

For patients to be included in the ORR, the CR or CRi needed to be confirmed at least 4 weeks after the initial assessment.

The threshold for success in Study B2202 was based on a 20% ORR (95% CI: 10, 34) reported in a previous study for a similar patient population treated with clofarabine (Jeha et al 2006). An ORR of 45% that excluded a $\leq$ 20% ORR at the 0.025 significance level was considered to provide meaningful efficacy in this highly refractory patient population.

A key secondary endpoint of Study B2202 was the proportion of patients achieving a BOR of CR or CRi with an MRD-negative bone marrow (i.e. MRD <0.01%) by central analysis using flow cytometry. MRD negativity has been recognized as a surrogate measure correlating with

long-term clinical benefit in pediatric patients with ALL (van Dongen et al 2015). MRD negativity was assessed similarly in Study B2205J as a secondary endpoint.

In Study B2101J, ORR was a secondary endpoint; the primary endpoints were the safety, feasibility of manufacture, and long-term persistence of tisagenlecleucel.

Table 4-3 Efficacy endpoints and statistical methodology

Study B2202	Statistical methodology
Primary endpoint	
ORR per IRC assessment within 3 months post-tisagenlecleucel infusion	Analyzed by testing the null hypothesis (ORR ≤ 20%) (Jeha et al 2006) against the alternative hypothesis (ORR >20%) at an overall one-sided 2.5% level of significance. ORR was summarized along with the 2-sided exact Clopper-Pearson CIs with an α level determined by the O'Brien Fleming α-spending function according to Lan and DeMets (1983) to account for the interim analysis once 50 patients had completed 3 months of follow-up or had discontinued for any reason
Key secondary endpoints	
ORR within 3 months post-tisagenlecleucel infusion for all patients who received tisagenlecleucel from a manufacturing facility in the US	Only performed when the primary objective had been met for the family-wise type I error rate to be controlled at a one-sided 2.5% level under the hierarchical testing scheme. Type I error probability was controlled using an O'Brien-Fleming α-spending function at a 2.5% level of significance.
BOR (CR/CRi) in patients with MRD-negative bone marrow within 3 months both among all patients and among patients with US-manufactured product (as two separate key secondary endpoints)	Analyzed by testing the null hypothesis (MRD-negative response ≤ 15%) (O'Brien et al 2013, Topp et al 2015) against the alternative hypothesis (MRD-negative response >15%) at an overall one-sided 2.5% level of significance.
Other efficacy endpoints included:	
DoR, RFS, EFS, OS, and PROs	Analyses of other endpoints were descriptive and included summary statistics (e.g. means, standard deviations, 95% CIs, if applicable). Confidence intervals, Kaplan-Meier curves, and median time to event were presented for time-to-event variables, if appropriate.

BOR Best overall response; CI confidence interval; CR Complete remission; CRi Complete remission with incomplete blood count recovery; DoR Duration of remission; EFS Event-free survival; IRC Independent Review Committee; MRD Minimal residual disease; ORR Overall remission rate; OS Overall survival; PROs Patient-reported outcomes; RFS Relapse-free survival

Table 4-4 Overall disease response classification at a given evaluation time

Response category	Definition used in Studies B2202, B2205J, and B2101J
CR	All the following criteria must be met: **Bone marrow** <5% blasts **Peripheral blood** Neutrophils >1.0×10^9 /L Platelets >100×10^9 /L Circulating blasts <1% **Extramedullary disease** [1] No clinical evidence of extramedullary disease (by physical examination and CNS symptom assessment) If additional assessments are performed (e.g. CSF assessment by LP, CNS imaging, biopsy, etc), results must show remission

Response category	Definition used in Studies B2202, B2205J, and B2101J
	Transfusion independency No platelet and/or neutrophil transfusions ≤ 7 days before the date of the peripheral blood sample for disease assessment
CRi	All criteria for CR as defined above are met, except that the following exist: Neutrophils ≤ 1.0×10^9 /L, or Platelets ≤ 100×10^9 /L, or Platelet and/or neutrophil transfusions ≤ 7 days before the date of the peripheral blood sample for disease assessment
No remission	Failure to attain the criteria needed for any response categories or relapse
Relapsed disease	Only in patients who achieved CR or CRi and who have: Reappearance of blasts in the blood (≥ 1%), or Reappearance of blasts in bone marrow (≥ 5%), or (Re-)appearance of any extramedullary disease after CR or CRi
Unknown	'Unknown' is assigned in cases where the baseline assessment or the response assessment is not done, incomplete, indeterminate, or not performed within the respective time frame If there is evidence of relapse, the overall response will be assessed as 'relapsed disease' with the relapsed component alone

CNS Central nervous system; CR Complete remission; CRi Complete remission with incomplete blood count recovery; CSF Cerebrospinal fluid; LP Lumbar puncture

[1] Compared to Studies B2202 and B2205J, assessment of extramedullary disease in Study B2101J was not required at each efficacy evaluation unless there was clinical evidence of extramedullary disease that warranted assessment

Independent Review Committee

The IRC for Study B2202 consisted of three core members external to Novartis with experience and expertise in the clinical management of patients with ALL. The IRC functioned independently to assess disease responses according to the Novartis guidelines for response assessment in ALL, based on laboratory results of bone marrow, blood, cerebrospinal fluid, and physical examination status documented by the Investigator (Table 4-4). The IRC performed assessments of disease status for each patient using data listings generated from the clinical database. No information regarding Investigator response assessments were shared with the IRC. An independent statistician and an independent data manager from a Contract Research Organization were appointed to facilitate the IRC review and liaise with the Novartis Study Lead for information requests. If requested by the IRC, additional information could be provided (e.g. imaging scans and/or reports; original pathology reports for blood, bone marrow, cerebrospinal fluid, etc).

For the BOR to be classified as CR or CRi within 3 months, the onset of remission must be within 3 months of infusion, and there must be no clinical evidence of relapse as assessed by peripheral blood and extramedullary disease assessment (physical examination and CNS symptom assessment) at a minimum of 4 weeks (28 days) after the initial achievement of CR or CRi. The BOR would be 'No response' if the patient failed to maintain CR or CRi for ≥ 28 days. The BOR would be 'Unknown' if there was no subsequent adequate response assessment after the initial CR or CRi.

4.3.3 Adequacy of safety evaluations

The safety of tisagenlecleucel was evaluated on the basis of the:

- Frequency, type, severity, and causal relationship of AEs to study treatment
- Frequency of deaths, SAEs, and other clinically significant AEs
- Frequency and type of AEs in key demographic subgroups (age, gender, race, and region) and by baseline disease characteristics
- Changes in laboratory variables, with particular attention to grade 3/4 laboratory abnormalities

Adverse events and laboratory parameters were graded using the National Cancer Institute (NCI)'s Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03, for all studies. Furthermore, AEs were classified according to the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.1; MedDRA usage was uniform and consistent. The grading of CRS and graft-versus-host disease (GvHD) was based on protocol-specific grading scales.

The clinical monitoring for AEs was considered adequate for the expected toxicities associated with tisagenlecleucel therapy. In addition to the standard safety evaluations outlined above, several AE categories warranting closer scrutiny were pre-identified during the development program. These AESIs were selected based on the mechanism of action of tisagenlecleucel and biological plausibility, as well as nonclinical observations.

5 Efficacy of tisagenlecleucel in B-cell ALL

5.1 Efficacy results in supportive Studies B2101J and B2205J

Encouraging data (in the form of promising and durable efficacy) were initially forthcoming from Study B2101J conducted at the Children's Hospital of Philadelphia (see following sections for further details). The experience from this initial trial subsequently led to the initiation of further trials to confirm the safety and effectiveness of tisagenlecleucel in both multicenter (Study B2205J; US) and international (Study B2202; US, Canada, EU, Australia, and Japan) settings.

5.1.1 Patient populations – Studies B2101J and B2205J

Patients recruited to Studies B2101J and B2205J were representative of the clinical population of pediatric and young adult patients with r/r B-cell ALL (see Section 2.1).

- The focus of the Study B2101J analysis was on 55 patients with non-CNS3 ALL (i.e. no active CNS involvement) who received treatment with tisagenlecleucel (Table 5-1). Median age was 11 years (range: 1 to 24). All patients had a Karnofsky/Lansky performance status score of ≥ 50%. Patients were heavily pretreated (89.1% had received ≥ 3 and 16.4% had received ≥ 6 prior regimens), and 63.6% had undergone prior SCT. Available mutation data were limited.
- Study B2205J enrolled 35 pediatric and young adult patients with r/r B-cell ALL, with a median age of 12 years (range: 3 to 25) (Table 5-1). Twenty-nine patients were infused with tisagenlecleucel; all had a Karnofsky/Lansky performance status score ≥ 50%, and included individuals with high-risk mutations. Patients had received a median of 3 prior therapies (range: 1 to 9) and 58.6% had failed prior allo-SCT.

Table 5-1 Demographic and baseline characteristics – Studies B2101J and B2205J

Demographic variable	Study B2101J Non-CNS3 ALL N=55		Study B2205J N=29	
Median age, years (range)	11.0	(1-24)	12.0	(3-25)
Age category, years - n (%)				
<10	26	(47.3)	9	(31.0)
≥ 10 to <18	24	(43.6)	13	(44.8)
≥ 18	5	(9.1)	7	(24.1)
Gender - n (%)				
Male - n (%)	30	(54.5)	11	(37.9)
Female	25	(45.5)	18	(62.1)
Race - n (%)				
White	46	(83.6)	25	(86.2)
Asian	2	(3.6)	2	(6.9)
Other	7	(12.7)	2	(6.9)
Prior stem-cell transplantation	35	(63.6)	17	(58.6)
Median no. of previous lines of therapy (range)	4.0	(1-8)	3.0	(1-9)
Disease status - n (%) [1]				
Relapsed disease	52	(94.5)	25	(86.2)
Primary refractory	3	(5.5)	2	(6.9)
Chemorefractory	NR		2	(6.9)

Non-CNS3 ALL Active CNS involvement excluded; NR Not reported

[1] Data on disease status were collected differently in Study B2101J, with 'primary refractory' reflecting patients who failed their first-line of therapy

5.1.2 Magnitude of treatment effect – Studies B2101J and B2205J

Results from Studies B2101J and B2205J provide supportive evidence for the efficacy of tisagenlecleucel in the treatment of pediatric and young adult patients with r/r B-cell ALL (Table 5-2).

- CR or CRi at Day 28 was a secondary endpoint in Study B2101J, where tumor responses were assessed by the Investigator. The ORR at Day 28 was high (94.5%) and most of the patients (89.1%) were in remission with MRD-negative bone marrow. Median DoR (Figure 5-1) and event-free survival (EFS) were not reached. The estimated probability of being relapse-free was 83.8% at Month 3 and 73.4% at Month 6.
  Of note, Study B2101J has the longest follow-up time of the trials conducted with tisagenlecleucel, with a maximum follow-up extending to 40.5 months. The estimated probabilities of survival at Months 6, 12, and 24 were 85.1%, 80.6%, and 62.6%, respectively (Figure 5-2).
- Study B2205J met its primary endpoint at an interim analysis, with an ORR per IRC within 6 months post-tisagenlecleucel infusion of 69.0% (95% CI: 49.2, 84.7). The primary endpoint exceeded the prespecified threshold (null hypothesis) of 20% with a p-value of <0.0001. The ORR assessed by the Investigator was identical to that reported by the IRC. Results of the secondary efficacy endpoints supported the clinical benefit observed with the primary endpoint. The depth and quality of the ORR was demonstrated

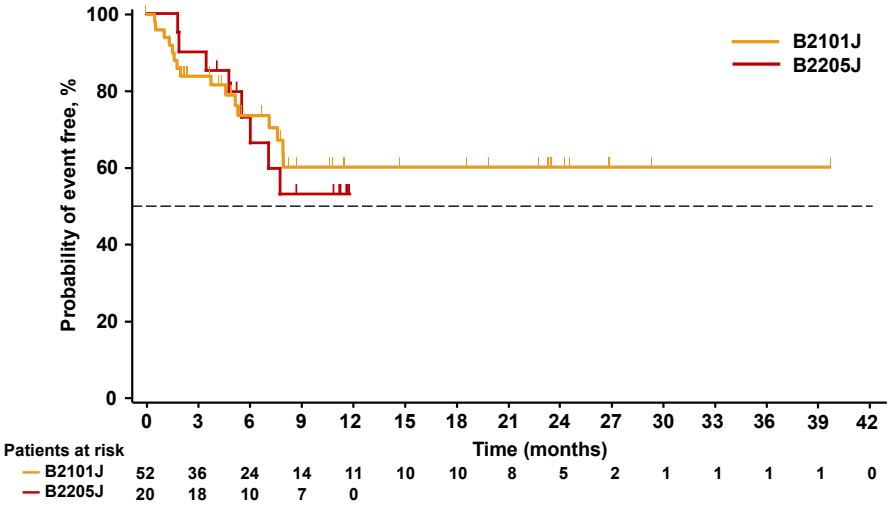
by a sensitive MRD bone marrow assessment. The proportion of patients with BOR of CR or CRi and MRD-negative bone marrow was 62.1% (95% CI: 42.3, 79.3). Most of the patients with a BOR of CR or CRi (90%) had MRD-negative bone marrow. Medians for DoR and OS have not been reached. The estimated probability of remaining in remission at Month 6 was 66.4%, and the estimated EFS probability at Month 6 was 55.0%. The probability of survival was 75.7% at Month 6.

Table 5-2 Overview of key efficacy endpoints – Studies B2101J and B2205J

	Study B2101J Non-CNS3 ALL N=55		Study B2205J N=29	
ORR within 3 months				
ORR (CR plus CRi) – n (%)	52	(94.5)	20	(69.0)
95% confidence interval	84.9, 98.9		49.2, 84.7	
p-value	N/A		<0.0001	
CR	38	(69.1)	18	(62.1)
CRi	14	(25.5)	2	(6.9)
NR	3	(5.5)	7	(24.1)
Unknown	0		2	(6.9)
Response with MRD-negative bone marrow				
ORR with MRD-negative bone marrow – n (%)	49	(89.1)	18	(62.1)
95% confidence interval	77.8, 95.9		42.3, 79.3	
Duration of remission				
Events/responders (%)	16/52	(30.8)	8/20	(40.0)
Median DoR (mo) (95% CI)	NR		NR	
KM estimate of remission at Month 6 (%) (95% CI)	73.4	(57.7, 84.1)	66.4	(39.3, 83.6)
Event-free survival				
Events/all patients (%)	19/55	(34.5)	17/29	(58.6)
Median EFS (mo) (95% CI)	NR		6.9	(1.5, NE)
KM estimate of EFS at Month 6 (%) (95% CI)	74.6	(60.2, 84.5)	55.0	(35.3, 70.9)
Overall survival				
Events/all patients (%)	15/55	(27.3)	10/29	(34.5)
Median OS (mo) (95% CI)	32.7	(21.0, NE)	NR	
KM estimate of OS at Month 6 (%) (95% CI)	85.1	(72.4, 92.3)	75.7	(55.7, 87.6)

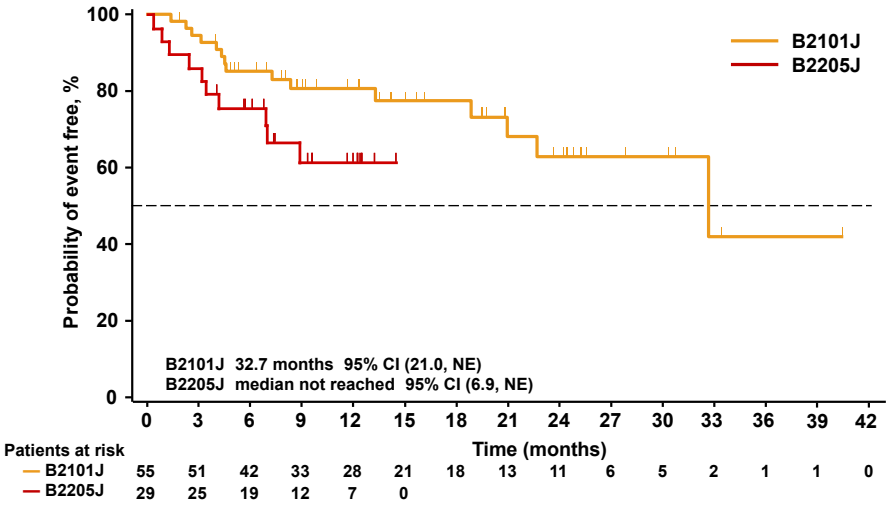
CI Confidence interval; CR Complete remission; CRi Complete remission with incomplete blood count recovery; DoR Duration of remission; EFS Event-free survival; FAS Full Analysis Set; KM Kaplan-Meier; MRD Minimal residual disease; NE Not estimable; Non-CNS3 ALL Active CNS involvement excluded; NR Not reached; NR No remission; ORR Overall remission rate

Figure 5-1 Duration of remission – Studies B2101J and B2205J



CI Confidence interval; CR Complete remission; CRi Complete remission with incomplete blood count recovery; DoR Duration of remission; NE Not estimable

Figure 5-2 Overall survival – Studies B2101J and B2205J



CI Confidence interval; NE Not estimable; OS Overall survival

5.2 Pivotal Study B2202

5.2.1 Disposition of patients – Study B2202

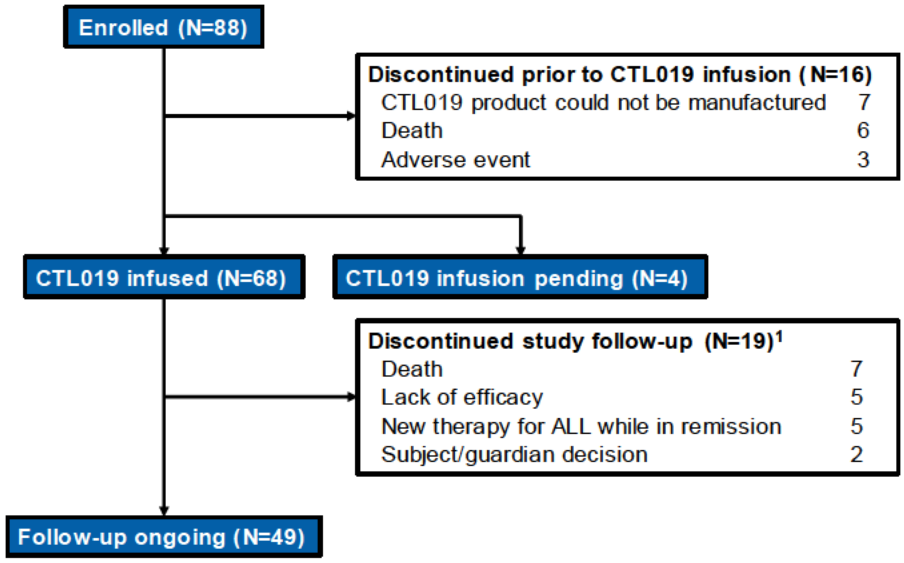
One-hundred-seven patients were screened for entry to Study B2202 between the first-patient first-visit (FPFV) of 08-Apr-2015 and the data cut-off date of 23-Nov-2016. Eleven patients were deemed to be ineligible: 8 patients who were in complete remission (with <5% blasts in their bone marrow), 2 patients with a life expectancy of ≤ 12 weeks, 1 patient with inadequate organ function, and 1 patient with no CD19 tumor expression in bone marrow or peripheral blood (note: patients may have had multiple reasons for screen failure). A further 4 patients satisfied the eligibility criteria but were not enrolled: 2 of whom died, 1 due to physician

decision, and 1 due to a leukapheresis product issue. For the remaining 4 patients, the screening process was ongoing at the time of the data cut-off.

Of the 88 patients who were enrolled (where enrollment required all clinical eligibility criteria to be met and the leukapheresis product to be accepted at the manufacturing facility), 68 (77.3%) were administered tisagenlecleucel. Sixteen patients (18.2%) discontinued prior to the infusion (see Figure 5-3) and the infusion was pending at the time of the data cut-off for 4 patients. Among the 68 patients who received tisagenlecleucel, the median time from infusion to the data cut-off was 8.76 months (range: 0.3 to 18.5). The median time from enrollment to tisagenlecleucel infusion was 43.5 days (range: 30 to 105).

As of the data cut-off date, 49 patients remained on-study with follow-up ongoing and 19 patients had discontinued study follow-up. All patients continue to be followed for survival.

Figure 5-3 Patient disposition – Study B2202



ALL Acute lymphoblastic leukemia

[1] Post-discontinuation, patients are followed for survival status

5.2.2 Dose administration – Study B2202

Sixty-five of the 68 patients (95.6%) who were administered tisagenlecleucel also received lymphodepleting chemotherapy after enrollment and prior to the tisagenlecleucel infusion.

The median dose of tisagenlecleucel infused in the pivotal study was 1.0×10^8 transduced viable T cells (range: 0.03 to 2.6×10^8). The median weight-adjusted dose of tisagenlecleucel administered was 3.0×10^6 transduced viable T cells/kg (range: 0.2 to 5.4×10^6).

5.2.3 Analysis sets – Study B2202

The following analysis sets were used:

- Enrolled Set: comprising all patients who enrolled (N=88). Enrollment was defined as patients having met all entry criteria, with the subsequent receipt and acceptance of patients' leukapheresis product by the manufacturing facility.

- Full Analysis Set (FAS): defined as all patients who received at least one tisagenlecleucel infusion (N=68)
- Efficacy Analysis Set (EAS): defined as all patients who received tisagenlecleucel infusion at least 3 months prior to the data cut-off date (N=63). This EAS was used for the final analysis of ORR in patients treated with US-manufactured product.
- Interim Efficacy Analysis Set (IEAS): comprising the first 50 patients in Study B2202 who received tisagenlecleucel infusion (used for the primary efficacy analysis)
- Per-protocol Set (PPS): a subset of the EAS who were compliant with major requirements of the protocol (N=57)
- Safety Set: this was the same as the FAS (N=68), and was used to summarize drug exposure

The study is currently ongoing to enable evaluation of patients infused with tisagenlecleucel manufactured by the EU facility.

5.2.4 Patient population – Study B2202

Demographic and baseline disease characteristics reflected the target pediatric and young adult patient population with r/r B-cell ALL for whom the drug is intended (Table 5-3 and Table 5-4). The study enrolled patients with r/r B-cell ALL across 25 centers in the US, Canada, the EU, Australia, and Japan. Patients were aged 3 to 23 years (median: 12) with a Karnofsky/Lansky performance status score of ≥ 50%. The population consisted of patients with high-risk mutations following a median of 3 prior therapies (range: 1 to 8), with 58.8% of patients having failed prior allo-SCT.

Table 5-3 Demographic and baseline characteristics – Study B2202

Demographic variable	All infused patients N=68	
Median age, years (range)	12.0	(3-23)
Age category, years - n (%)		
<10	28	(41.2)
≥ 10 to <18	28	(41.2)
≥ 18	12	(17.6)
Gender - n (%)		
Male	38	(55.9)
Female	30	(44.1)
Race - n (%)		
White	51	(75.0)
Asian	6	(8.8)
Other	11	(16.2)
Prior allogeneic stem-cell transplantation - n (%)		
0	28	(41.2)
1	35	(51.5)
2	5	(7.4)
Median no. of previous lines of therapy (range)	3	(1-8)

Demographic variable	All infused patients N=68	
Disease status - n (%)		
Relapsed disease	54	(79.4)
Chemorefractory	8	(11.8)
Primary refractory	6	(8.8)

Table 5-4 Baseline disease characteristics – Study B2202

Characteristic	All infused patients N=68	
Median morphologic blast count in bone marrow (%) (range)	73.2	(5.0-98.5)
CNS status classification - n (%)		
CNS1	57	(83.8)
CNS2	9	(13.2)
CNS3	1	(1.5)
Unknown	1	(1.5)
Extramedullary disease upon physical examination - n (%)		
Yes	7	(10.3)
No	61	(89.7)

CNS Central nervous system: CNS1 No detectable leukemia cells in the CSF; CNS2 Very low levels of leukemia cells in the CSF; CNS3 Active CNS involvement; CSF Cerebrospinal fluid

5.2.5 Interim analysis – Study B2202

Results of the interim analysis indicated that the trial met its primary endpoint:

- ORR per IRC assessment was 82.0% (95% CI: 68.6, 91.4; p<0.0001)
  - Investigator assessments of ORR were 100% concordant with the IRC analyses

Key secondary endpoints were also met at this analysis:

- As of the data cut-off date, all tisagenlecleucel product was manufactured at the Morris Plains facility, NJ. The results of the first key secondary endpoint (ORR within 3 months in patients treated with US-manufactured product) were therefore identical to the primary efficacy endpoint while the results of the third key secondary endpoint (BOR of CR or CRi with an MRD-negative bone marrow in patients treated with US-manufactured product within this 3-month period) were the same as those for the second key secondary endpoint (BOR of CR or CRi with an MRD-negative bone marrow based on all manufacturing facilities) (see below).
- 82.0% of patients (95% CI: 68.6, 91.4; p<0.0001) achieved a BOR of CR or CRi per IRC assessment within 3 months of tisagenlecleucel infusion with an MRD-negative bone marrow

5.2.6 Updated primary efficacy endpoint: ORR – Study B2202

Results of the final analysis of ORR in patients treated with US-manufactured product provide compelling evidence for the efficacy of tisagenlecleucel in the treatment of pediatric and young adult patients with r/r B-cell ALL, with Study B2202 meeting its primary endpoint of

IRC-assessed ORR. The ORR per IRC assessment was 82.5% (95% CI: 70.9, 90.9; p<0.0001) (Table 5-5 and Figure 5-4). Of note, most of the patients attained CR as opposed to CRi.

Table 5-5 Overall remission rate per IRC assessment – Study B2202 (EAS)

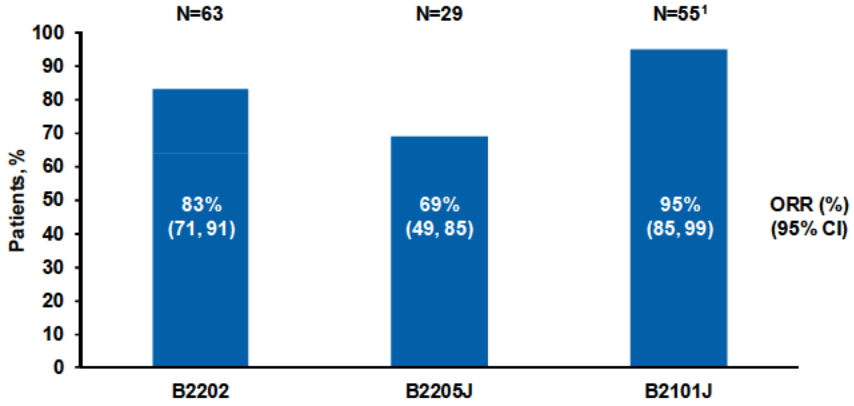
	Efficacy Analysis Set N=63			
Efficacy variables	**n**	**(%)**	**95% CI**	**p-value**
Primary				
Overall remission rate (CR plus CRi) within 3 mo	52	(82.5)	70.9, 90.9	<0.0001 [1]
Best overall response (BOR)				
CR	40	(63.5)		
CRi	12	(19.0)		
Key secondary				
Achieved BOR of CR or CRi within 3 mo with MRD-negative bone marrow	52	(82.5)	70.9, 90.9	<0.0001 [1]

CI Confidence interval; CR Complete remission; CRi Complete remission with incomplete blood count recovery; EAS Efficacy Analysis Set; IRC Independent Review Committee; MRD Minimal residual disease

[1] No formal significance testing was conducted as this endpoint was met at the interim analysis. The nominal p-value is presented.

Furthermore, Investigator assessments of ORR were 100% concordant with the IRC analyses.

Figure 5-4 Consistent overall remission rate across Studies B2202, B2205J, and B2101J



CI Confidence interval; ORR Overall remission rate

[1] Overall remission rates at Day 28 in patients with non-CNS3 ALL (i.e. no active CNS involvement)

5.2.6.1 Sensitivity and subgroup analyses – Study B2202

Multiple preplanned sensitivity analyses demonstrated that the observed ORR benefit was robust and consistent, with ORRs ranging from 65.8% to 84.2% and with the lower bounds of the 95% CI exceeding 20% in all cases:

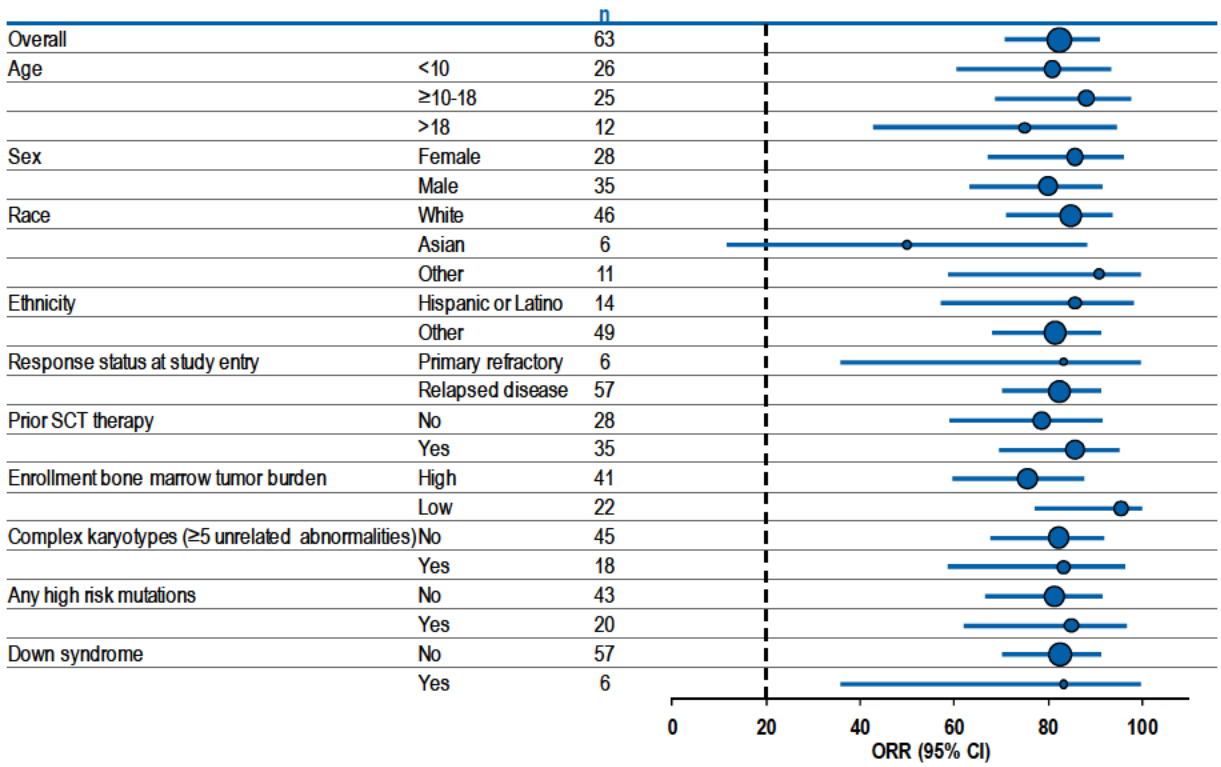
- Efficacy Analysis Set (EAS): ORR 82.5% (95% CI: 70.9, 90.9)
- Per-protocol Set (PPS): ORR 84.2% (95% CI: 72.1, 92.5)

- EAS plus enrolled patients who discontinued prior to tisagenlecleucel infusion: ORR 65.8% (95% CI: 54.3, 76.1)

A homogeneous treatment effect was also evident across all subgroups (Figure 5-5), including patients with a poor prognosis with standard therapy.

- Patients aged <10 years (n=26): ORR 80.8% (95% CI: 60.6, 93.4)
- Patients aged ≥ 10 to 18 years (n=25): ORR 88.0% (95% CI: 68.8, 97.5)
- Patients aged > 18 years (n=12): ORR 75.0% (95% CI: 42.8, 94.5)
- Patients with primary refractory disease (n=6): ORR 83.3% (95% CI: 35.9, 99.6)
- Patients with prior allo-SCT (n=35): ORR 85.7% (95% CI: 69.7, 95.2)
- Patients carrying high-risk mutations (n=20); ORR 85.0% (95% CI: 62.1, 96.8)
- Patients with Down syndrome (n=6): ORR 83.3% (95% CI: 35.9, 99.6)

Figure 5-5 ORR treatment effect for patient subgroups – Study B2202 (EAS)



CI Confidence interval; EAS Efficacy Analysis Set; ORR Overall remission rate; SCT Allogeneic stem-cell transplantation

5.2.7 Updated secondary efficacy endpoints – Study B2202

The clinical benefit of tisagenlecleucel reflected in the primary endpoint was further supported by the key and other secondary endpoints.

5.2.7.1 Key secondary endpoint: remission rate in patients with MRD-negative bone marrow – Study B2202

The study met its key secondary objective of IRC-assessed bone marrow MRD status within 3 months post-tisagenlecleucel infusion in patients who received tisagenlecleucel. All patients who achieved remission attained an MRD-negative bone marrow; 52 of 63 infused patients (82.5%; 95% CI: 70.9, 90.9) achieved a BOR of CR or CRi per IRC assessment within 3 months post-tisagenlecleucel infusion with an MRD-negative bone marrow (Table 5-5).

5.2.7.2 Day 28 disease response and MRD status – Study B2202

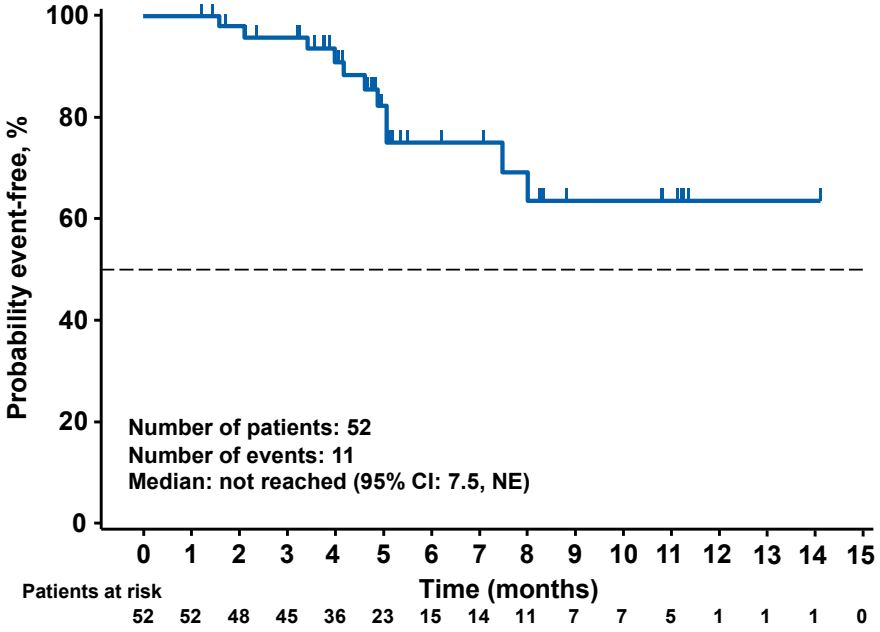
Onset of remission was observed at Day 28 for the majority of responders. The proportion of patients with a BOR of CR or CRi at Day 28 per IRC assessment was 84.1% (95% CI: 72.7, 92.1) among all infused patients. All patients with a BOR of CR or CRi were also in MRD negative remission at Day 28 with the exception of a single patient who attained MRD remission within 3 months.

5.2.7.3 Duration of remission – Study B2202

Eleven of the 52 patients (21.2%) in the EAS who achieved a BOR of CR or CRi per IRC assessment either experienced a relapse or died due to their underlying leukemia prior to the data cut-off (Table 1-2, Figure 5-6, and Figure 5-7). These relapses occurred in a range between 48 and 243 days following the onset of remission.

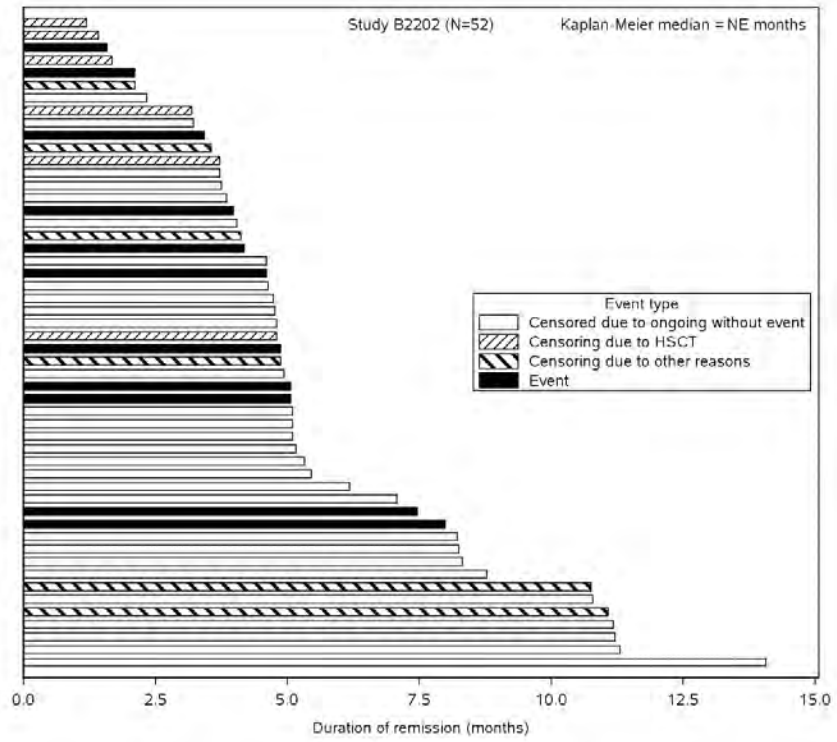
Median DoR was not reached. Responses were ongoing in 29 patients, with individual DoRs ranging from 36+ to 428+ days (Figure 5-7). The DoR was censored for 12 patients, including for 11 patients while still in remission (6 of whom underwent SCT, 4 of whom were administered humanized CD19 CAR-T cells, and 1 who received ponatinib) and 1 patient for whom an adequate assessment was no longer available. The estimated relapse-free rate among responders per IRC review was 75.4% (95% CI: 57.2, 86.7) at Month 6 and 63.8% (95% CI: 41.5, 79.4) at Months 9 and 12.

Figure 5-6 Duration of remission – Study B2202 (EAS)



CI Confidence interval; EAS Efficacy Analysis Set; NE Not estimable

Figure 5-7 Individual durations of remission for patients with a best overall response of CR or CRi – Study B2202

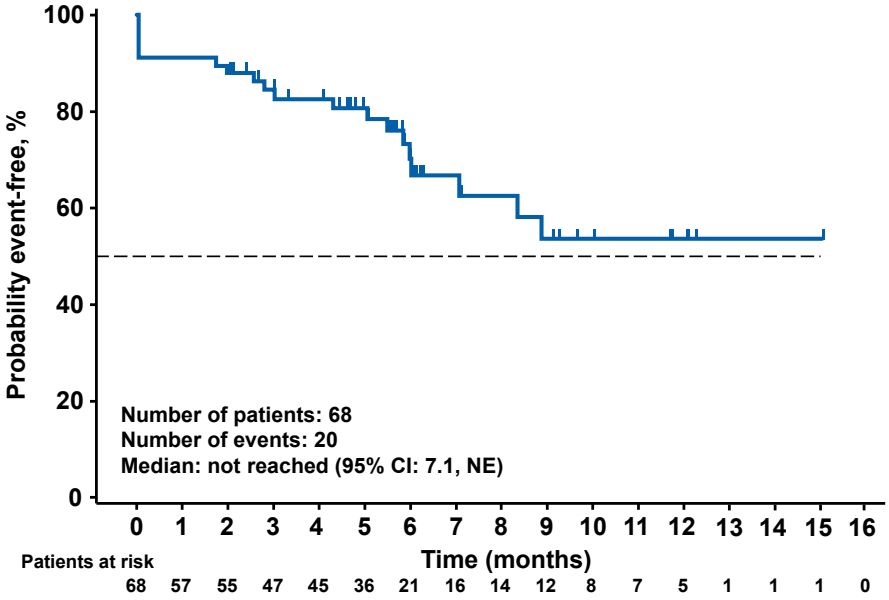


CR Complete remission; CRi Complete remission with incomplete blood count recovery; NE Not estimable (not reached); HSCT Allogeneic stem-cell transplantation

5.2.7.4 Event-free survival – Study B2202

Twenty of the 68 patients (29.4%) in the FAS experienced a relapse or treatment failure (with patients undergoing SCT censored in the analysis), or died due to any cause prior to the data cut-off (Table 1-2 and Figure 5-8). Median EFS was not reached. The estimated event-free probability was 70.2% (95% CI: 55.1, 81.1) at Month 6 and 53.7% (95% CI: 35.1, 69.2) at Months 9 and 12 per IRC assessment.

Figure 5-8 Event-free survival – Study B2202 (FAS)



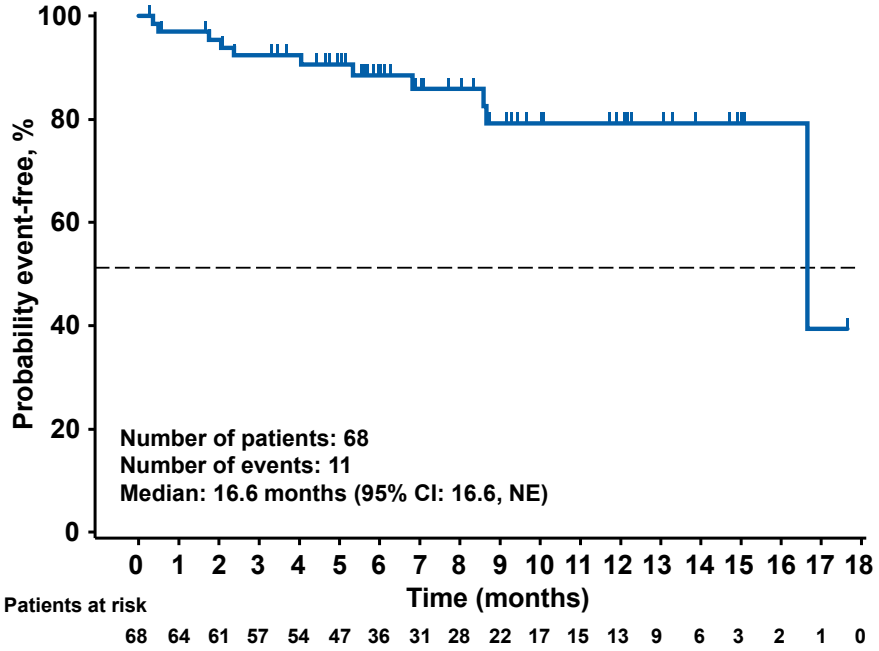
CI Confidence interval; FAS Full Analysis Set; NE Not estimable

5.2.7.5 Overall survival – Study B2202

Eleven of the 68 patients (16.2%) in the FAS died post-tisagenlecleucel infusion (Table 1-2 and Figure 5-9). Median OS was estimated to be 16.6 months; however, this median value should be interpreted with caution because approximately 84% of the patients were still alive (and therefore censored in the analysis) at the time of the data cut-off and only 2 patients were at risk at timepoints beyond 16 months.

Of note, the probability of being alive was 88.6% (95% CI: 77.4, 94.4) at Month 6 and 79.2% (95% CI: 63.8, 88.8) at Months 9 and 12.

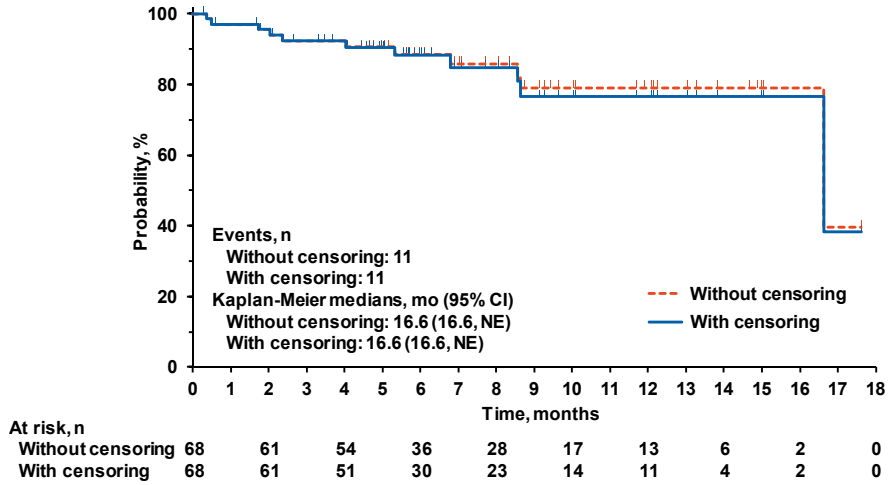
Figure 5-9 Overall survival – Study B2202 (FAS)



CI Confidence interval; FAS Full Analysis Set; NE Not estimable

Tisagenlecleucel is intended to be a definitive therapy, with only 7 patients electing to receive an allo-SCT while in remission. An additional 2 patients received allo-SCT following relapse, although the follow-up for these patients was limited. The impact of allo-SCT on the OS curve was minimal, as seen in Figure 5-10, with the respective curves with and without censoring for SCT almost superimposable.

Figure 5-10 Overall survival with and without censoring for SCT – Study B2202 (FAS)



CI Confidence interval; FAS Full Analysis Set; NE Not estimable; SCT Allogeneic stem-cell transplantation

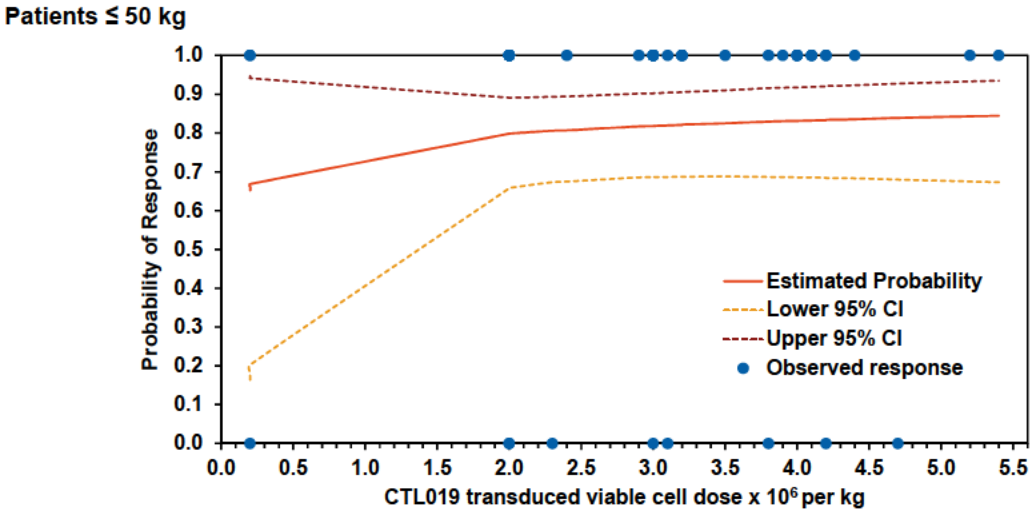
5.3 Dose-response analyses

Relationship between tisagenlecleucel dose and Day 28 response

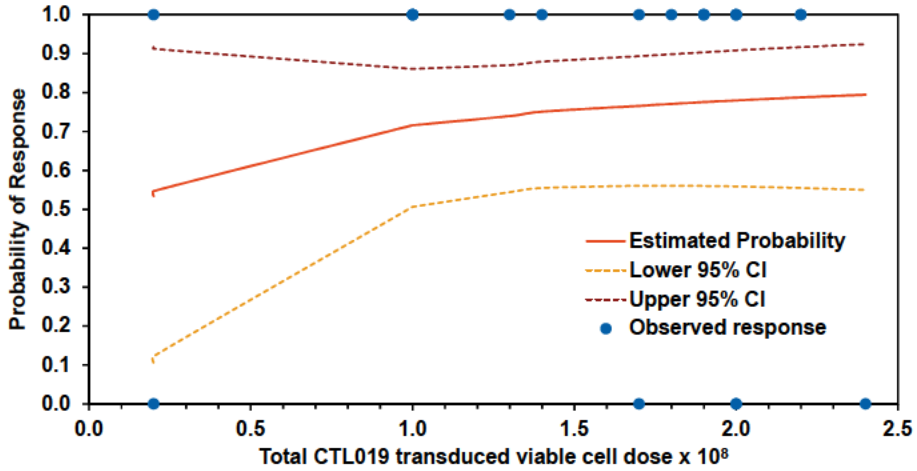
Clinical responses were observed across the entire range of doses tested in both weight categories (≤ 50 kg and >50 kg) and although there was limited experience at lower doses, clinical benefit was still evident.

- Trends favoring an increased probability of response with increasing cell dose were observed (Figure 5-11) in a logistic regression model (including log-dose, study, weight category, study by log-dose, and weight by log-dose in the model) for:
  - Patients ≤ 50 kg where the dose-response curve showed a moderate increasing trend in the probability of response for doses up to 2.0×10^6 transduced viable T cells/kg, with an apparent plateau for higher doses
  - Patients >50 kg for doses up to 1.0×10^8 total transduced viable T cells, with an apparent plateau for higher doses
- Responses were also observed at the lowest doses tested (0.2×10^6 transduced viable T cells/kg for patients ≤ 50 kg and 0.1×10^8 total transduced viable T cells for patients >50 kg)

Figure 5-11 Dose response logistic regression analyses, overlaid with observed proportions – Study B2202 (Safety Analysis Set)



Patients >50 kg



CI Confidence interval

Limited data are available for the left-hand tails of these regression analyses; these aspects should therefore be interpreted with caution

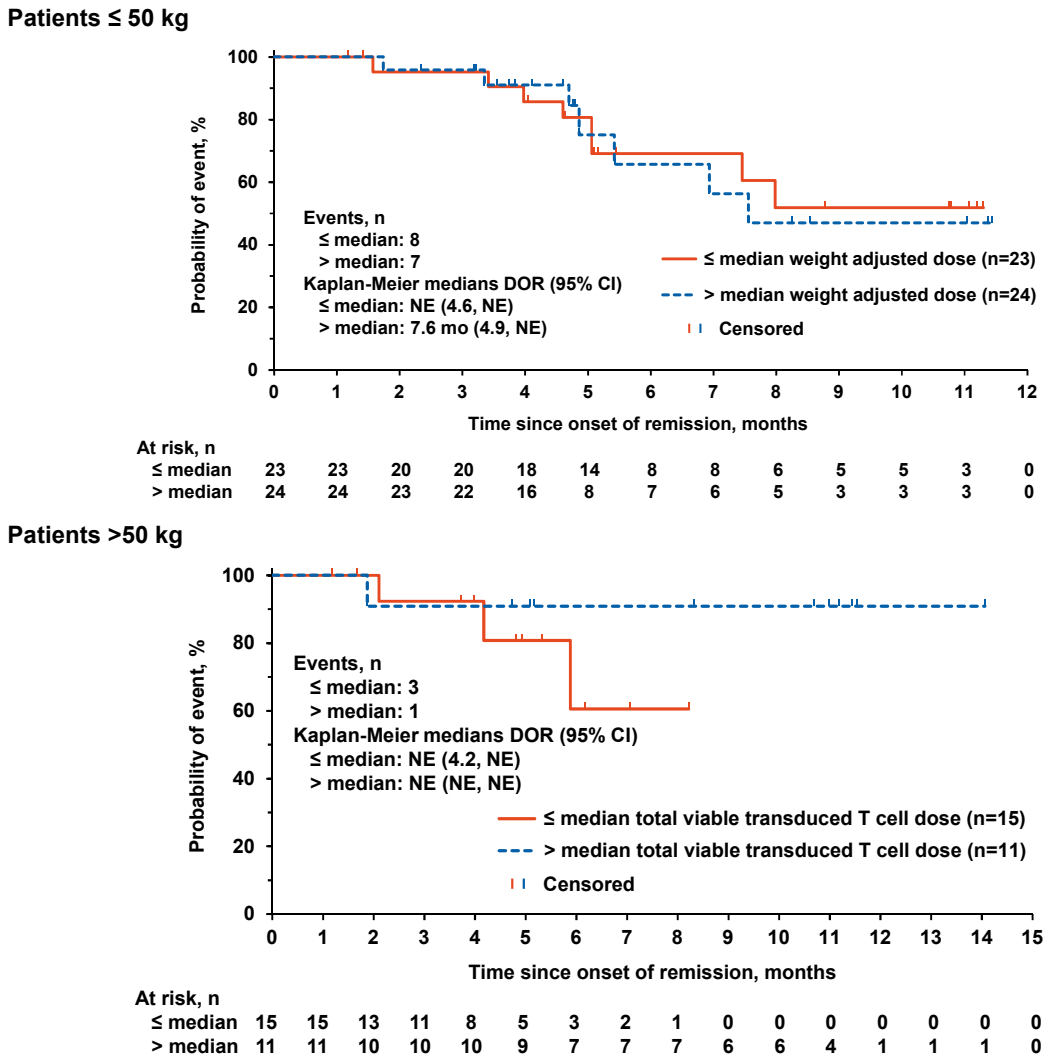
Categories: 1=responders; 0=non-responders/unknown

Note: 46 patients in Study B2202 weighed ≤ 50 kg (37 responders and 9 non-responders/unknown) and 22 patients weighed >50 kg (17 responders and 5 non-responders/unknown). The full statistical model included the 97 patients from Studies B2202 and B2205J with appropriate adjustments for study and weight category but only those in the appropriate subgroup are represented on these plots.

Results of an evaluation of response by dose quartile showed that ORRs were similar irrespective of the dose administered.

Limited conclusions can be derived from the Kaplan-Meier plots of DoR by median of exposure due to the small numbers of events and patients. Overall, there was a small separation in the Kaplan-Meier curves suggesting patients with AUC0-28d greater than the median may have a more durable remission relative to patients with AUC0-28d less than the median, although this difference was minimal. AUC0-84d did not appear to impact DoR. Based on Cox regression analysis of the pooled data from Studies B2202 and B2205J, the risk of relapse did not appear to be impacted by exposure as measured by AUC0-84d.

Figure 5-12 Duration of remission by median of exposure – Studies B2202 and B2205J



CI Confidence interval; DOR Duration of remission; NE Not estimable

Dose-cellular kinetic analyses were summarized in Section 3.2.

5.4 Long-term data

5.4.1 Persistence of efficacy and long-term benefit

Persistence of efficacy and long-term clinical benefit appears to be evident. Unlike most of the currently available anti-neoplastic agents, tisagenlecleucel is administered either as a single infusion (Studies B2205J and B2202) or as a limited number of infusions (Study B2101J). Treatment with tisagenlecleucel leads to a rapid response with onset of remission in responding patients by Day 28. The fact that median DoR has not been reached in any of the three studies conducted to date, and especially in Study B2101J where the maximum follow-up is 43.5 months, suggests long-term persistence of efficacy in this population (Figure 5-1).

Follow-up of patients in Study B2101J was longer than for patients in Studies B2205J and B2202. With a median follow-up from the time of the initial infusion to the data cut-off of 18.6 months in Study B2101J, the estimated probability of being relapse-free at Months 6 and 9 was 73.4% and 60.0%, respectively, after which time point a plateau appeared to be reached. Median OS was 32.7 months (95% CI: 21.0, not estimable [NE]) in this trial. The estimated probability of survival at Months 12 and 24 was 80.6% (95% CI: 66.8, 89.1) and 62.6% (95% CI: 42.1, 77.7), respectively. These results are suggestive of the long-term clinical benefit of tisagenlecleucel in pediatric and young adult patients with r/r B-cell ALL.

Additionally, the persistence of tisagenlecleucel is further supported by the on-target effect of tisagenlecleucel on the elimination of normal, CD19+ B-cells. Responding patients experienced continued B-cell aplasia indicating the long-term effect of tisagenlecleucel. Persistence of the tisagenlecleucel transgene in the peripheral blood of responding patients for up to 780 days, with B-cell aplasia ongoing for >3 years, is further evidence for the long-term effect. In contrast, non-responding patients showed variable or little decline in normal CD19+ B cells in peripheral blood.

6 Safety of tisagenlecleucel in B-cell ALL

6.1 Safety population

One-hundred-twenty-three patients were enrolled in the single-arm, multicenter Studies B2202 and B2205J (the Safety Pool), in which pediatric and young adult patients with r/r B-cell ALL were to be administered a single dose of tisagenlecleucel. The safety evaluation is based primarily on data from the 97 patients infused in Studies B2202 (N=68) and B2205J (N=29). These data were pooled to facilitate a more robust safety assessment in a larger pool of patients with a longer duration of follow-up. Studies B2202 and B2205J had near-identical study designs, enrolled identical patient populations, and used standardized lymphodepleting regimens (Figure 4-1 and Table 4-2).

Safety data from the 55 pediatric and young adult patients with r/r B-cell ALL who were administered tisagenlecleucel in Study B2101J were considered supportive. Further supportive data were available from adult patients with ALL and CLL in Studies B2102J (N=20) and A2201 (N=28), respectively, as well as all the available safety information from 14 other ongoing studies (from the Novartis safety database).

Safety management in the pivotal trial was emphasized with a robust and comprehensive training program initiated prior to patient enrollment commencing. This program covered the leukapheresis process and stem-cell laboratory, as well as the clinical centers (this included, but was not limited to, CRS management guidelines). Educational materials were also provided for the patients and their families. As each product is unique to a specific patient, the identity of the patient material is verified at each step in the manufacturing process. Robust systems and labeling were used to ensure that the chain of identity was maintained. Prior to infusion, all patients underwent influenza testing, an assessment of both their clinical status and disease status, and an evaluation of their laboratory data. Patients with uncontrolled infections or evidence of accelerating leukemia were excluded from participating in these studies.

6.2 Patient exposure – Studies B2202 and B2205J

Of the 123 patients enrolled in Studies B2202 and B2205J, 22 patients discontinued prior to tisagenlecleucel infusion, 97 patients were infused, and the infusion was pending for the remaining 4 (Table 6-1). The median duration between tisagenlecleucel infusion and the data cut-off date was 8.76 months (range: 0.3 to 18.5) for Study B2202 and 6.37 months (range: 0.4 to 14.0) for Study B2205J.

Table 6-1 Overview of patients enrolled but not infused – Studies B2202 and B2205J

Disposition Reason	All patients N=123 n (%)	
Enrolled	123	(100.0)
Discontinued prior to tisagenlecleucel infusion	22	(17.9)
Death	10	(8.1) [1]
Tisagenlecleucel product-related issue	9	(7.3)
Adverse event	3	(2.4) [2]
Tisagenlecleucel infusion pending	4	(3.3)

[1] Deaths were attributed to acute lymphoblastic leukemia (n=5), infection (n=3), and organ failure (n=2)
[2] Adverse events leading to discontinuation prior to infusion were infections (n=2) and graft-versus-host disease (n=1)

6.2.1 Lymphodepleting chemotherapy – Studies B2202 and B2205J

Overall, 92 patients received lymphodepleting chemotherapy in the Safety Pool, where fludarabine plus cyclophosphamide-based regimens were the agents of choice, and were subsequently administered tisagenlecleucel. The lymphodepleting regimen consisted of:

- Fludarabine (30 mg/m^2 iv daily for 4 days) and cyclophosphamide (500 mg/m^2 iv daily for 2 days starting with the first dose of fludarabine)

The following lymphodepleting regimen was used if a patient had a previous grade 4 hemorrhagic cystitis with cyclophosphamide or had demonstrated a chemorefractory state to a cyclophosphamide-containing regimen administered shortly before lymphodepleting chemotherapy:

- Cytarabine (500 mg/m^2 iv daily for 2 days) and etoposide (150 mg/m^2 iv daily for 3 days starting with the first dose of cytarabine)

Lymphodepleting chemotherapy was not required if a patient presented with a WBC count ≤ 1000 cells/μL in the week prior to tisagenlecleucel infusion.

Lymphocyte-depleting chemotherapy was not part of the investigational protocol in Study B2101J; it was chosen and administered by the primary/referring oncologist. The choice of chemotherapy depended on the patient's underlying disease and prior therapies, but the majority of patients received fludarabine and cyclophosphamide.

6.2.2 Tisagenlecleucel infusion – Studies B2202 and B2205J

In the Safety Pool, the median dose of tisagenlecleucel infused was 1.0×10^8 transduced viable T cells (range: 3.0×10^6 to 2.6×10^8); this corresponded to a median weight-adjusted dose of 3.2×10^6 transduced viable T cells/kg (range: 0.2×10^6 to 5.4×10^6).

Of note, the dose range in Study B2101J was broader (up to a total dose of 1.5×10^7 to 5×10^9 total T cells), with the total dose split across multiple infusions (fractions of 10%, 30%, and 60% of the total dose) within the first 28 days. A number of patients in Study B2101J also received a re-infusion after Day 28.

6.3 Adverse events – Studies B2202 and B2205J

The nature and incidence of AEs reported in the Safety Pool were similar and consistent with those reported in the earlier Study B2101J (Section 6.6). Results in the following sections focus on the Safety Pool.

6.3.1 Frequent adverse events – Studies B2202 and B2205J

6.3.1.1 Adverse events prior to tisagenlecleucel infusion during the pre-treatment period – Studies B2202 and B2205J

Patients in the Safety Pool experienced a broad range of AEs even prior to treatment with lymphodepleting chemotherapy or tisagenlecleucel infusion (Table 6-2). Adverse events were consistent with those expected in patients receiving chemotherapy for r/r B-cell ALL. These events were manageable per the relevant product information.

Table 6-2 Adverse events following enrollment and prior to commencing lymphodepleting chemotherapy occurring in at least 5% of patients by grade – Studies B2202 and B2205J

	All enrolled patients N=123					
	All grades		Grade 3		Grade 4	
Preferred term	n	(%)	n	(%)	n	(%)
No. of patients with at least 1 AE	**109**	**(88.6)**	**40**	**(32.5)**	**52**	**(42.3)**
Non-hematologic AEs						
Pyrexia	21	(17.1)	4	(3.3)	0	
Nausea	14	(11.4)	4	(3.3)	0	
Stomatitis	10	(8.1)	8	(6.5)	1	(0.8)
Hypotension	10	(8.1)	6	(4.9)	3	(2.4)
Pain in extremity	10	(8.1)	6	(4.9)	0	
Headache	10	(8.1)	5	(4.1)	0	
Hypoxia	10	(8.1)	3	(2.4)	1	(0.8)
Fatigue	10	(8.1)	1	(0.8)	0	
Decreased appetite	9	(7.3)	5	(4.1)	0	
Hypokalaemia	9	(7.3)	4	(3.3)	1	(0.8)
Abdominal pain	9	(7.3)	3	(2.4)	0	
Tachycardia	8	(6.5)	4	(3.3)	0	
Alanine aminotransferase increased	7	(5.7)	4	(3.3)	0	

	All enrolled patients N=123					
	All grades		Grade 3		Grade 4	
Preferred term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
C-reactive protein increased	7	(5.7)	2	(1.6)	1	(0.8)
Constipation	7	(5.7)	0		0	
Hypertension	7	(5.7)	0		0	
Hematologic AEs						
Anaemia	30	(24.4)	22	(17.9)	1	(0.8)
Febrile neutropenia	26	(21.1)	25	(20.3)	1	(0.8)
Thrombocytopenia	15	(12.2)	4	(3.3)	9	(7.3)
Neutropenia	12	(9.8)	1	(0.8)	10	(8.1)
Neutrophil count decreased	11	(8.9)	3	(2.4)	8	(6.5)
Platelet count decreased	10	(8.1)	0		10	(8.1)
White blood cell count decreased	7	(5.7)	0		6	(4.9)

AE Adverse event

6.3.1.2 Adverse events prior to tisagenlecleucel infusion during lymphodepleting chemotherapy – Studies B2202 and B2205J

Among the 94 patients who received lymphodepleting chemotherapy, 79.8% reported ≥ 1 AE; grade 3 and 4 AEs were reported in 11.7% and 27.7% of patients, respectively (Table 6-3). As expected for patients undergoing lymphodepleting chemotherapy, the most commonly reported events were WBC count decreased (12.8%, primarily grade 4), nausea (11.7%), anemia (10.6%), pyrexia (10.6%), neutrophil count decreased (8.5%, mostly grade 4), and febrile neutropenia (7.4%, all grade 3).

Table 6-3 Adverse events during lymphodepleting chemotherapy occurring in at least 5% of patients by grade – Studies B2202 and B2205J

	All patients who received lymphodepleting chemotherapy N=94					
	All grades		Grade 3		Grade 4	
Preferred term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
No. of patients with at least 1 AE	**75**	**(79.8)**	**11**	**(11.7)**	**26**	**(27.7)**
Non-hematologic AEs						
Nausea	11	(11.7)	1	(1.1)	0	
Pyrexia	10	(10.6)	0		0	
Hypokalaemia	6	(6.4)	3	(3.2)	3	(3.2)
Hypotension	6	(6.4)	3	(3.2)	0	
Alanine aminotransferase increased	6	(6.4)	1	(1.1)	1	(1.1)
Vomiting	6	(6.4)	1	(1.1)	0	
Abdominal pain	5	(5.3)	0		0	
Decreased appetite	5	(5.3)	0		0	
Hematologic AEs						
White blood cell count decreased	12	(12.8)	3	(3.2)	9	(9.6)
Anaemia	10	(10.6)	6	(6.4)	0	
Neutrophil count decreased	8	(8.5)	1	(1.1)	6	(6.4)

	All patients who received lymphodepleting chemotherapy N=94					
	All grades		Grade 3		Grade 4	
Preferred term	n	(%)	n	(%)	n	(%)
Febrile neutropenia	7	(7.4)	7	(7.4)	0	
Platelet count decreased	5	(5.3)	1	(1.1)	4	(4.3)

AE Adverse event

6.3.1.3 Adverse events post-tisagenlecleucel infusion – Studies B2202 and B2205J

Cytokine release syndrome was the most commonly reported AE (in 81.4% of patients, and reported as grade 3/4 in 44.3%). Cytokine release syndrome AEs are discussed further in the sections that follow.

Hematologic events, frequently grade 3/4 in nature, can be expected in this population receiving treatment with lymphodepleting chemotherapy and T-cell therapy (Brudno and Kochenderfer 2016), and were among the more commonly reported events: febrile neutropenia (36.1%), anemia (33.0%), WBC count decreased (30.9%), neutrophil count decreased (28.9%), and platelet count decreased (27.8%) (Table 1-4).

Transaminase increases (aspartate transaminase [AST] and alanine transaminase [ALT] elevations) were observed in approximately 30% of patients (AST: 30.9%; ALT: 29.9%), and were often reported as grade 3/4 (AST: 18.6%; ALT: 14.4%). Events of pyrexia (41.2%), decreased appetite (39.2%), hypogammaglobulinemia (34.0%), vomiting (34.0%), headache (33.0%), hypotension (32.0%), and nausea (32.0%) were also reported in ≥ 30% of patients (Table 1-4).

The most commonly reported AEs suspected to be related to study treatment were CRS (81.4%), hypogammaglobulinemia (29.9%), febrile neutropenia (28.9%), hypotension (28.9%), pyrexia (28.9%), and decreased appetite (25.8%).

Adverse events by time period (initial 8 weeks post-infusion vs. 8 weeks to 1 year)

Analyses of AEs by time period (as tisagenlecleucel therapy consists of a single treatment for the Safety Pool) indicated that AEs were more frequently reported within the initial 8-week period post-tisagenlecleucel infusion, with 97.9% of patients reporting ≥ 1 AE and 82.5% of patients with grade 3/4 AEs. Subsequently, incidence rates were markedly reduced in the period from 8 weeks to 1 year, with 82.5% of patients reporting ≥ 1 AE and 41.3% of patients with grade 3/4 AEs (Table 6-4).

Of note, CRS was reported exclusively within the initial 8-week period post-tisagenlecleucel infusion. Gastrointestinal events (including nausea, vomiting, and diarrhea) were primarily reported in the initial 8-week period post-infusion (and were most commonly grade 1/2 in intensity); however, incidence rates of approximately 10% were also seen in the period from 8 weeks to 1 year.

Hematologic AEs were also mostly reported within 8 weeks of tisagenlecleucel infusion.

Table 6-4 Adverse events post-tisagenlecleucel infusion occurring in at least 20% of patients by grade and time period – Studies B2202 and B2205J

	All infused patients					
	Initial 8-week period N=97			8 weeks to 1 year N=80		
Preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
No. of patients with at least 1 AE	**95 (97.9)**	**23 (23.7)**	**57 (58.8)**	**66 (82.5)**	**19 (23.8)**	**14 (17.5)**
Non-hematologic AEs						
Cytokine release syndrome	79 (81.4)	19 (19.6)	24 (24.7)	0	0	0
Decreased appetite	32 (33.0)	19 (19.6)	1 (1.0)	6 (7.5)	0	0
Pyrexia	32 (33.0)	8 (8.2)	3 (3.1)	11 (13.8)	2 (2.5)	0
Vomiting	31 (32.0)	3 (3.1)	0	7 (8.8)	2 (2.5)	0
AST increased	30 (30.9)	11 (11.3)	7 (7.2)	3 (3.8)	2 (2.5)	0
Hypotension	30 (30.9)	10 (10.3)	13 (13.4)	2 (2.5)	1 (1.3)	1 (1.3)
Headache	29 (29.9)	2 (2.1)	0	9 (11.3)	0	0
ALT increased	28 (28.9)	12 (12.4)	0	5 (6.3)	4 (5.0)	0
Hypokalaemia	26 (26.8)	11 (11.3)	2 (2.1)	2 (2.5)	1 (1.3)	1 (1.3)
Nausea	26 (26.8)	5 (5.2)	0	9 (11.3)	2 (2.5)	0
Tachycardia	25 (25.8)	4 (4.1)	1 (1.0)	2 (2.5)	0	0
Diarrhoea	23 (23.7)	1 (1.0)	0	8 (10.0)	1 (1.3)	0
Hypoxia	21 (21.6)	9 (9.3)	7 (7.2)	2 (2.5)	2 (2.5)	0
Hypophosphataemia	20 (20.6)	10 (10.3)	1 (1.0)	1 (1.3)	1 (1.3)	0
Hematologic AEs						
Febrile neutropenia	35 (36.1)	33 (34.0)	2 (2.1)	3 (3.8)	3 (3.8)	0
Anaemia	31 (32.0)	14 (14.4)	1 (1.0)	4 (5.0)	2 (2.5)	0
White blood cell count decreased	29 (29.9)	5 (5.2)	17 (17.5)	8 (10.0)	2 (2.5)	1 (1.3)
Platelet count decreased	25 (25.8)	4 (4.1)	13 (13.4)	5 (6.3)	1 (1.3)	1 (1.3)
Neutrophil count decreased	24 (24.7)	2 (2.1)	19 (19.6)	12 (15.0)	4 (5.0)	5 (6.3)
Hypogammaglobulinaemia	22 (22.7)	3 (3.1)	0	13 (16.3)	1 (1.3)	0

AE Adverse event; ALT Alanine aminotransferase; AST Aspartate aminotransferase

Events suspected to be drug related

Adverse events that were suspected by the Investigator to be drug related were also reviewed and summarized (Table 6-5). Again, the striking difference between the initial 8-week period and the subsequent period from 8 weeks to 1 year should be noted.

Table 6-5 Adverse events post-infusion suspected to be related to tisagenlecleucel occurring in at least 20% of patients by grade and time period – Studies B2202 and B2205J

	All infused patients					
	Initial 8-week period N=97			8 weeks to 1 year N=80		
Preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
No. of patients with at least 1 AE suspected to be related to tisagenlecleucel	**89 (91.8)**	**25 (25.8)**	**45 (46.4)**	**38 (47.5)**	**10 (12.5)**	**5 (6.3)**
Non-hematologic AEs						
Cytokine release syndrome	79 (81.4)	19 (19.6)	24 (24.7)	0	0	0
Hypotension	28 (28.9)	9 (9.3)	12 (12.4)	0	0	0
Pyrexia	27 (27.8)	6 (6.2)	3 (3.1)	1 (1.3)	0	0
Decreased appetite	23 (23.7)	14 (14.4)	1 (1.0)	2 (2.5)	0	0
AST increased	23 (23.7)	8 (8.2)	6 (6.2)	3 (3.8)	2 (2.5)	0
ALT increased	21 (21.6)	10 (10.3)	0	2 (2.5)	2 (2.5)	0
Tachycardia	21 (21.6)	3 (3.1)	1 (1.0)	0	0	0
Vomiting	20 (20.6)	0	0	4 (5.0)	0	0
Hematologic AEs						
Febrile neutropenia	28 (28.9)	27 (27.8)	1 (1.0)	1 (1.3)	1 (1.3)	0
White blood cell count decreased	20 (20.6)	3 (3.1)	11 (11.3)	3 (3.8)	0	0

AE Adverse event; ALT Alanine aminotransferase; AST Aspartate aminotransferase

Further analysis of AEs beyond the initial 8-week period by causality shows that the incidence of events suspected to be related to tisagenlecleucel in the longer-term is low (Table 6-6).

Table 6-6 Adverse events within the period from 8 weeks to 1 year post-tisagenlecleucel infusion occurring in at least 5% of patients by grade and causal relationship – Studies B2202 and B2205J

	All infused patients					
	Irrespective of causality N=80			Suspected to be related N=80		
Preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
No. of patients with at least 1 AE	**66 (82.5)**	**19 (23.8)**	**14 (17.5)**	**38 (47.5)**	**10 (12.5)**	**5 (6.3)**
Non-hematologic AEs						
Pyrexia	11 (13.8)	2 (2.5)	0	1 (1.3)	0	0
Cough	10 (12.5)	0	0	4 (5.0)	0	0
Upper respiratory tract infection	9 (11.3)	4 (5.0)	0	2 (2.5)	1 (1.3)	0
Nausea	9 (11.3)	2 (2.5)	0	4 (5.0)	0	0
Headache	9 (11.3)	0	0	3 (3.8)	0	0
Diarrhoea	8 (10.0)	1 (1.3)	0	2 (2.5)	0	0
Vomiting	7 (8.8)	2 (2.5)	0	4 (5.0)	0	0
Pain in extremity	7 (8.8)	1 (1.3)	0	2 (2.5)	0	0
Decreased appetite	6 (7.5)	0	0	2 (2.5)	0	0
Fatigue	6 (7.5)	0	0	2 (2.5)	0	0

	All infused patients					
	Irrespective of causality N=80			Suspected to be related N=80		
Preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
ALT increased	5 (6.3)	4 (5.0)	0	2 (2.5)	2 (2.5)	0
Abdominal pain	5 (6.3)	1 (1.3)	0	2 (2.5)	0	0
Parainfluenzae virus infection	4 (5.0)	1 (1.3)	1 (1.3)	0	0	0
Nasal congestion	4 (5.0)	0	0	0	0	0
Hematologic AEs						
Hypogammaglobulinaemia	13 (16.3)	1 (1.3)	0	13 (16.3)	1 (1.3)	0
Neutrophil count decreased	12 (15.0)	4 (5.0)	5 (6.3)	8 (10.0)	2 (2.5)	3 (3.8)
White blood cell count decreased	8 (10.0)	2 (2.5)	1 (1.3)	3 (3.8)	0	0
Platelet count decreased	5 (6.3)	1 (1.3)	1 (1.3)	3 (3.8)	0	0
Anaemia	4 (5.0)	2 (2.5)	0	1 (1.3)	0	0
Lymphocyte count decreased	4 (5.0)	2 (2.5)	0	3 (3.8)	1 (1.3)	0

AE Adverse event; ALT Alanine aminotransferase

Grading (severity) of adverse events

The most common grade 3/4 events experienced during the initial 8-week period post-tisagenlecleucel infusion were CRS, febrile neutropenia, hypotension, decreased WBC count, decreased neutrophil count, and decreased appetite (Table 6-7). In the majority of cases, these events were suspected to be related to tisagenlecleucel.

Table 6-7 Grade 3/4 adverse events within the initial 8-week period post-tisagenlecleucel infusion occurring in at least 5% of patients by causal relationship – Studies B2202 and B2205J

	All infused patients			
	Irrespective of causality N=97		Suspected to be related N=97	
Preferred term	Grade 3 n (%)	Grade 4 n (%)	Grade 3 n (%)	Grade 4 n (%)
No. of patients with at least 1 AE	**23 (23.7)**	**57 (58.8)**	**25 (25.8)**	**45 (46.4)**
Non-hematologic AEs				
Cytokine release syndrome	19 (19.6)	24 (24.7)	19 (19.6)	24 (24.7)
Hypotension	10 (10.3)	13 (13.4)	9 (9.3)	12 (12.4)
Decreased appetite	19 (19.6)	1 (1.0)	14 (14.4)	1 (1.0)
AST increased	11 (11.3)	7 (7.2)	8 (8.2)	6 (6.2)
Hypoxia	9 (9.3)	7 (7.2)	8 (8.2)	5 (5.2)
Hypokalaemia	11 (11.3)	2 (2.1)	7 (7.2)	0
ALT increased	12 (12.4)	0	10 (10.3)	0
Hypophosphataemia	10 (10.3)	1 (1.0)	6 (6.2)	1 (1.0)
Pyrexia	8 (8.2)	3 (3.1)	6 (6.2)	3 (3.1)
Pulmonary oedema	8 (8.2)	2 (2.1)	6 (6.2)	1 (1.0)
Blood bilirubin increased	9 (9.3)	0	8 (8.2)	0
Acute kidney injury	3 (3.1)	6 (6.2)	3 (3.1)	5 (5.2)
Hypocalcaemia	6 (6.2)	0	4 (4.1)	0

	All infused patients			
	Irrespective of causality N=97		Suspected to be related N=97	
	Grade 3	Grade 4	Grade 3	Grade 4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Hyperglycaemia	5 (5.2)	0	2 (2.1)	0
Hypertension	5 (5.2)	0	1 (1.0)	0
Left ventricular dysfunction	5 (5.2)	0	4 (4.1)	0
Nausea	5 (5.2)	0	4 (4.1)	0
Tachypnoea	5 (5.2)	0	3 (3.1)	0
Blood creatinine increased	4 (4.1)	1 (1.0)	4 (4.1)	1 (1.0)
Dyspnoea	3 (3.1)	2 (2.1)	2 (2.1)	0
Respiratory failure	0	5 (5.2)	0	3 (3.1)
Hematologic AEs				
Febrile neutropenia	33 (34.0)	2 (2.1)	27 (27.8)	1 (1.0)
White blood cell count decreased	5 (5.2)	17 (17.5)	3 (3.1)	11 (11.3)
Neutrophil count decreased	2 (2.1)	19 (19.6)	1 (1.0)	11 (11.3)
Platelet count decreased	4 (4.1)	13 (13.4)	2 (2.1)	9 (9.3)
Lymphocyte count decreased	11 (11.3)	5 (5.2)	8 (8.2)	4 (4.1)
Anaemia	14 (14.4)	1 (1.0)	4 (4.1)	0
Thrombocytopenia	4 (4.1)	9 (9.3)	2 (2.1)	6 (6.2)
Neutropenia	2 (2.1)	6 (6.2)	2 (2.1)	3 (3.1)

AE Adverse event; ALT Alanine aminotransferase; AST Aspartate aminotransferase

Grade 3/4 events between Week 8 and 1 year were reported far less frequently than during the initial 8-week treatment period; this was especially the case for events suspected to be related to tisagenlecleucel (Table 6-8). This once again emphasizes that beyond the initial 8 weeks post-infusion, patients generally recover quickly.

Table 6-8 Grade 3/4 adverse events within the period from 8 weeks to 1 year post-tisagenlecleucel infusion occurring in at least 2.5% of patients by causal relationship – Studies B2202 and B2205J

	All infused patients			
	Irrespective of causality N=80		Suspected to be related N=80	
	Grade 3	Grade 4	Grade 3	Grade 4
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**
No. of patients with at least 1 AE	**19 (23.8)**	**14 (17.5)**	**10 (12.5)**	**5 (6.3)**
Non-hematologic AEs				
ALT increased	4 (5.0)	0	2 (2.5)	0
Upper respiratory tract infection	4 (5.0)	0	1 (1.3)	0
Metapneumovirus infection	3 (3.8)	0	0	0
AST increased	2 (2.5)	0	2 (2.5)	0
Haematuria	2 (2.5)	0	0	0
Hypoxia	2 (2.5)	0	0	0
Nausea	2 (2.5)	0	0	0
Pyrexia	2 (2.5)	0	0	0

	All infused patients							
	Irrespective of causality N=80				Suspected to be related N=80			
	Grade 3		Grade 4		Grade 3		Grade 4	
Preferred term	n (%)		n (%)		n (%)		n (%)	
Urinary tract infection	2	(2.5)	0		0		0	
Vomiting	2	(2.5)	0		0		0	
Blood uric acid increased	1	(1.3)	1	(1.3)	0		0	
Hypokalaemia	1	(1.3)	1	(1.3)	0		1	(1.3)
Hypotension	1	(1.3)	1	(1.3)	0		0	
Parainfluenzae virus infection	1	(1.3)	1	(1.3)	0		0	
Cardiac arrest	0		2	(2.5)	0		0	
Septic shock	0		2	(2.5)	0		0	
Hematologic AEs								
Neutrophil count decreased	4	(5.0)	5	(6.3)	2	(2.5)	3	(3.8)
Febrile neutropenia	3	(3.8)	0		1	(1.3)	0	
Anaemia	2	(2.5)	0		0		0	
Lymphocyte count decreased	2	(2.5)	0		1	(1.3)	0	
White blood cell count decreased	2	(2.5)	1	(1.3)	0		0	
Neutropenia	1	(1.3)	1	(1.3)	1	(1.3)	1	(1.3)
Platelet count decreased	1	(1.3)	1	(1.3)	0		0	

AE Adverse event; ALT Alanine aminotransferase; AST Aspartate aminotransferase

Adverse events by infused dose range

The median dose of tisagenlecleucel infused was 1.0×10^8 transduced viable T cells (range: 0.03×10^8 to 2.6×10^8) in the Safety Pool; this corresponded to a median weight-adjusted dose of 3.2×10^6 transduced viable T cells/kg (range: 0.2×10^6 to 5.4×10^6). The incidence and nature of events reported were generally similar irrespective of the dose infused. The severity of CRS, but not its rate of occurrence, appeared to increase with cell dose.

6.3.2 Deaths and other serious or clinically significant adverse events – Studies B2202 and B2205J

6.3.2.1 Deaths – Studies B2202 and B2205J

6.3.2.1.1 Deaths after enrollment and prior to tisagenlecleucel infusion – Studies B2202 and B2205J

Among the 123 patients enrolled in the Safety Pool, 16 (13.0%) died prior to tisagenlecleucel infusion (this includes patients who discontinued participation for whom survival follow-up was captured), including 8 due to disease progression. Of the remaining 8 patients, 6 died secondary to infection (3 due to pneumonia, 2 due to fungal infection, and 1 due to sepsis) and 2 died during the lymphodepletion period (1 due to multi-organ failure and 1 due to respiratory failure). This reflects the poor prognosis and high morbidity of patients with r/r B-cell ALL who are candidates for tisagenlecleucel therapy as well as the importance of controlling their disease and managing infections associated with the bridging chemotherapy.

6.3.2.1.2 Deaths within 30 days of tisagenlecleucel infusion – Studies B2202 and B2205J

Four patients died within the initial 30-day period post-tisagenlecleucel infusion (Table 6-9 and Table 6-10). This included 2 patients who died due to disease progression, 1 due to cerebral hemorrhage in the setting of DIC, and 1 due to embolic stroke from an intracardiac mucormycotic mass.

6.3.2.1.3 Deaths >30 days post-tisagenlecleucel infusion – Studies B2202 and B2205J

Seventeen patients died >30 days post-tisagenlecleucel infusion, including 14 due to disease progression. The remaining 3 patients all died due to infection: encephalitis, systemic mycosis, and a bacterial lower respiratory tract infection, respectively (Table 6-9 and Table 6-10), with the former 2 patients experiencing prolonged grade 3/4 neutropenia both prior to and post-tisagenlecleucel infusion.

Table 6-9 Overview of deaths and other serious or clinically significant adverse events – Studies B2202 and B2205J

	All infused patients					
	Within 30 days of infusion			>30 days post-infusion		
	B2202 N=68	B2205J N=29	All N=97	B2202 N=68	B2205J N=29	All N=97
Category	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Death post-infusion	**2 (2.9)**	**2 (6.9)**	**4 (4.1)**	**9 (13.2)**	**8 (27.6)**	**17 (17.5)**
Acute lymphoblastic leukemia	1 (1.5)	1 (3.4)	2 (2.1)	6 (8.8)	8 (27.6)	14 (14.4)
Cerebral haemorrhage	1 (1.5)	0	1 (1.0)	0	0	0
Embolic stroke	0	1 (3.4)	1 (1.0)	0	0	0
Encephalitis	0	0	0	1 (1.5)	0	1 (1.0)
Lower respiratory tract infection bacterial	0	0	0	1 (1.5)	0	1 (1.0)
Systemic mycosis	0	0	0	1 (1.5)	0	1 (1.0)
	Initial 8-week period			**8 weeks to 1 year**		
	B2202 N=68	**B2205J N=29**	**All N=97**	**B2202 N=59**	**B2205J N=21**	**All N=80**
Serious adverse event	**47 (69.1)**	**23 (79.3)**	**70 (72.2)**	**12 (20.3)**	**7 (33.3)**	**19 (23.8)**
Suspected to be drug related	45 (66.2)	22 (75.9)	67 (69.1)	1 (1.7)	2 (9.5)	3 (3.8)

Table 6-10 Deaths attributed to adverse events – Studies B2202 and B2205J

Patient number Age/gender/ days post-treatment	Cause of death System organ class MedDRA preferred term	Comments	Relationship (assessed by Investigator)
Deaths within 30 days			
B2205J-1006-001 8/F/25 days	Nervous system disorder Embolic stroke	Initially experienced grade 2 CRS, with fever resolving on Day 17 but followed by further episode of fever with onset on Day 21. On Day 23, new intermittent confusion occurred with brain CT showing hemorrhagic infarct, mass effect, and multiple lesions consistent with emboli with infarct. Cardiac echocardiogram showed left atrial mass. Neurologic and imaging findings rapidly progressed, support was withdrawn, and death occurred on Day 25. Autopsy findings confirmed left atrial thrombus with mucormycosis and multiple septic emboli.	Not suspected
B2202-1401-009 6/M/15 days	Nervous system disorder Cerebral hemorrhage	Patient experienced several SAEs suspected to be related to treatment: grade 2 CRS on Day 4, febrile neutropenia on Day 4, hypoxia requiring mechanical ventilation, hypotension requiring high-dose vasopressors, and grade 4 CRS on Day 7 requiring tocilizumab, steroids, and siltuximab, disseminated intravascular coagulation on Day 9 requiring blood product support, acute kidney injury on Day 12 requiring continuous veno-venous hemodiafiltration, and abdominal compartment syndrome on Day 13 requiring surgical release. On Day 15, the patient had a grade 4 cerebral hemorrhage with a fatal outcome.	Suspected
Deaths ≥ 30 days post-tisagenlecleucel infusion			
B2202-1100-002 4/F/30 days	Infections and infestations Encephalitis	Diagnosed with grade 4 encephalitis of indistinguishable causality that was fatal on Day 53 post-infusion. The event had an onset on Day 30 (with attribution by the Investigator of viral infection (HHV-6) or tisagenlecleucel or autoimmune) in the setting of prolonged neutropenia pre- and post-tisagenlecleucel infusion	Suspected
B2202-1401-001 6/M/506 days	Infections and infestations Lower respiratory tract infection bacterial	Discontinued the primary follow-up phase on Day 154 while in remission, upon receipt of lymphodepleting chemotherapy and subsequent humanized tisagenlecleucel, and entered the survival follow-up. Patient received an SCT 5 months later and died on Day 506 due to a bacterial lung infection in the context of chronic lung disease.	Not suspected
B2202-1404-003 18/F/64 days	Infections and infestations Systemic mycosis	Experienced grade 4 systemic mycosis that was fatal at Day 64 post-infusion. Prolonged cytopenia that predated the tisagenlecleucel infusion was a contributing factor. Other reported infections were also ongoing at the time of death.	Suspected

CRS Cytokine release syndrome; F Female; HHV-6 Human herpes virus-6; M Male; MedDRA Medical Dictionary for Regulatory Activities; SCT Stem-cell transplantation

6.3.2.2 Other serious or clinically significant adverse events – Studies B2202 and B2205J

6.3.2.2.1 Serious adverse events prior to tisagenlecleucel infusion – Studies B2202 and B2205J

Prior to lymphodepleting chemotherapy and tisagenlecleucel infusion, SAEs were reported in 65 of 123 enrolled patients (52.8%). Febrile neutropenia (12.2%), pyrexia (6.5%), and hypotension (4.9%) were the most commonly reported SAEs. All other events were reported in ≤ 4 patients.

Ten patients experienced SAEs during the lymphodepletion period.

6.3.2.2.2 Serious adverse events post-tisagenlecleucel infusion

Serious adverse events were reported in 76.3% of patients post-tisagenlecleucel infusion; this high frequency is primarily attributable to the proportion of patients with CRS (64.9%) (Table 6-11). Grade 3/4 febrile neutropenia was reported in 24.7% of patients. Grade 3/4 hypotension was reported in 12.4% of patients, and is a known consequence of CRS.

Table 6-11 Serious adverse events post-tisagenlecleucel infusion by grade and time period – Studies B2202 and B2205J

	All infused patients					
	Initial 8-week period N=97			8 weeks to 1 year N=80		
Preferred term	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Patients with at least 1 SAE	**70 (72.2)**	**27 (27.8)**	**36 (37.1)**	**19 (23.8)**	**13 (16.3)**	**6 (7.5)**
Cytokine release syndrome	63 (64.9)	18 (18.6)	24 (24.7)	0	0	0
Febrile neutropenia	23 (23.7)	22 (22.7)	1 (1.0)	3 (3.8)	3 (3.8)	0
Hypotension	12 (12.4)	3 (3.1)	9 (9.3)	1 (1.3)	0	1 (1.3)
Pyrexia	5 (5.2)	0	0	3 (3.8)	1 (1.3)	0
Hypoxia	5 (5.2)	2 (2.1)	3 (3.1)	1 (1.3)	1 (1.3)	0
Acute kidney injury	5 (5.2)	2 (2.1)	3 (3.1)	1 (1.3)	0	1 (1.3)
Respiratory failure	4 (4.1)	0	4 (4.1)	0	0	0
Pleural effusion	3 (3.1)	1 (1.0)	1 (1.0)	0	0	0
Cardiac arrest	1 (1.0)	0	1 (1.0)	2 (2.5)	0	2 (2.5)
Upper respiratory tract infection	0	0	0	4 (5.0)	4 (5.0)	0

SAE Serious adverse event

Of note, SAEs were more commonly reported within the initial 8-week period post-infusion than in the subsequent period from >8 weeks to 1 year (72.2% vs. 23.8%) (Table 6-9).

Cytokine release syndrome events deemed to be serious were all considered to be related to tisagenlecleucel therapy. Serious adverse events suspected to be related to tisagenlecleucel were reported in 3 patients (3.8%) in the period from >8 weeks to 1 year: these were single cases of febrile neutropenia, upper respiratory tract infection, and GvHD in the gastrointestinal tract.

Hospitalizations in Study B2202

Healthcare resource utilization data regarding hospitalizations were captured from the day of Screening in Study B2202 up to Month 2, with the exception of hospitalizations due to elective or pre-planned treatment, social reasons and respite care, and treatment occurring on an emergency outpatient basis that did not result in hospital admission.

- Fifty patients (73.5%) were administered tisagenlecleucel while hospitalized (the remaining 26.5% of patients were administered tisagenlecleucel on an out-patient basis)
- Sixty-four patients (94.1%) were admitted to the hospital at one or more timepoints, with most patients requiring either 1 (47.1%) or 2 hospital stays (35.3%). Among patients who were hospitalized, the median duration of hospitalization was 28.5 days (range: 3 to 161).
- Thirty-five patients (51.5%) required admittance to the ICU; the median duration of ICU stays was 7 days (range: 1 to 51) for these patients.

6.3.2.2.3 Adverse events of special interest – Studies B2202 and B2205J

Toxicities associated with T-cell directed therapies, some of which can be severe or fatal, include: B-cell aplasia, CRS and macrophage activation syndrome (MAS), infections, cytopenias, neurological events, and TLS. These class effects have been observed with anti-CD3 and anti-CD28 antibodies (Chatenoud et al 1990, Suntharalingam et al 2006), bispecific T cell engager peptides such as blinatumomab (Grupp et al 2013, Topp et al 2015), T-cell replete SCT (Abboud et al 2016), and CAR T-cells directed toward various tumor antigens (Ruella and June 2016). These effects are primarily attributed to the expansion and activation of T cells and macrophages with resulting local and systemic cytokine production and tumor cell killing.

The overall pattern of AESIs associated with tisagenlecleucel infusion in the Safety Pool was consistent with the safety profile observed in Study B2101J (Table 6-12). Each of these categories of events are discussed further here; these are well characterized events with the use of tisagenlecleucel which can in general be effectively managed with appropriate site training.

Table 6-12 AESIs within the initial 8 weeks post-infusion – Studies B2202 and B2205J

	All infused patients N=97					
	All grades		Grade 3		Grade 4	
AESI category	n	(%)	n	(%)	n	(%)
Cytokine release syndrome	79	(81.4)	19	(19.6)	24	(24.7)
Infections	43	(44.3)	18	(18.6)	3	(3.1)
Neurological events [1]	39	(40.2)	11	(11.3)	0	
Febrile neutropenia	35	(36.1)	33	(34.0)	2	(2.1)
Hematopoietic cytopenias (not resolved by Day 28)	34	(35.1)	13	(13.4)	16	(16.5)
Tumor lysis syndrome	3	(3.1)	3	(3.1)	0	

AESI Adverse event of special interest; MedDRA Medical Dictionary for Regulatory Activities; SMQ Standard MedDRA query

[1] Includes events in the non-infectious encephalopathy/delirium SMQ

Cytokine-release syndrome

Cytokine release syndrome is a systemic inflammatory response caused when cytokines are released by activated T cells, which has been observed in other types of T-cell directed therapies. Cytokine release syndrome is an on-target toxicity resulting from the expected expansion and activation of modified T-cells and related killing of normal and malignant tumor cells.

Clinical manifestations of CRS include high fevers, rigors, fatigue, anorexia, nausea, vomiting, diarrhea, diaphoresis, headache, encephalopathy, myalgia/arthralgia, rash, hypotension (occasionally requiring vasopressor support), capillary leak, tachypnea, hypoxia (occasionally requiring ventilator support), and evidence of DIC as well as MAS, which may be partly driven by elevated levels of IL-6 as well as other cytokines. Cytokine release syndrome and MAS have been effectively managed in the majority of patients with supportive care and anti-IL-6 cytokine-directed therapy with tocilizumab and siltuximab leading to rapid resolution; associated symptoms are reversible in the majority of patients (Maude et al 2014, Gill and June 2015). Tisagenlecleucel-associated MAS/hemophagocytic lymphohistiocytosis (HLH) in this setting has also been associated with striking elevations in ferritin and low levels of fibrinogen (Grupp et al 2013).

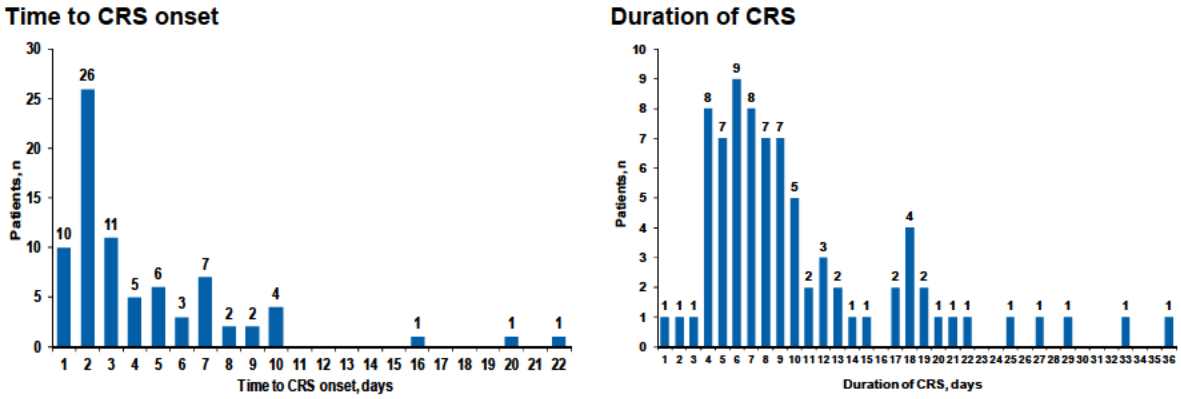
Cytokine release syndrome was reported in 81.4% of patients (grade 3/4 in 44.3%), with all events occurring within 8 weeks post-tisagenlecleucel infusion; 64.9% of patients had an SAE of CRS. Importantly, there were no fatalities attributed to refractory CRS in this trial. Onset occurred after a median of 3.0 days after infusion, although for 1 patient this was as late as Day 22 (Table 6-13 and Figure 6-1). The median duration of CRS was 8 days. Approximately 44% of patients were admitted to the ICU for the treatment of CRS, where the median duration of the ICU stay was 8 days. Anti-cytokine therapy was administered to 34.0% of patients resulting in CRS improvement or resolution. Supportive care included vasopressor use and ventilatory support. Dialysis was also initiated in some patients, mostly for the control of fluid volume.

Table 6-13 Cytokine release syndrome – Studies B2202 and B2205J

	All infused patients N=97	
No. of patients with CRS - n (%)	79	(81.4)
Median time to onset of CRS, days (range) [1]	3.0	(1-22)
Median duration of CRS, days (range)	8.0	(1-36)
Admitted to ICU - n (%)	43	(44.3)
Median duration of ICU stay, days (range) [2]	8.0	(1-34)
Systemic anti-cytokine therapy - n (%)	33	(34.0)
High-dose vasopressors - n (%)	26	(26.8)
Invasive ventilation (intubation) - n (%)	16	(16.5)
Dialysis - n (%)	11	(11.3)

CRS Cytokine release syndrome; ICU Intensive care unit
[1] Among patients with CRS
[2] Among patients admitted to the ICU

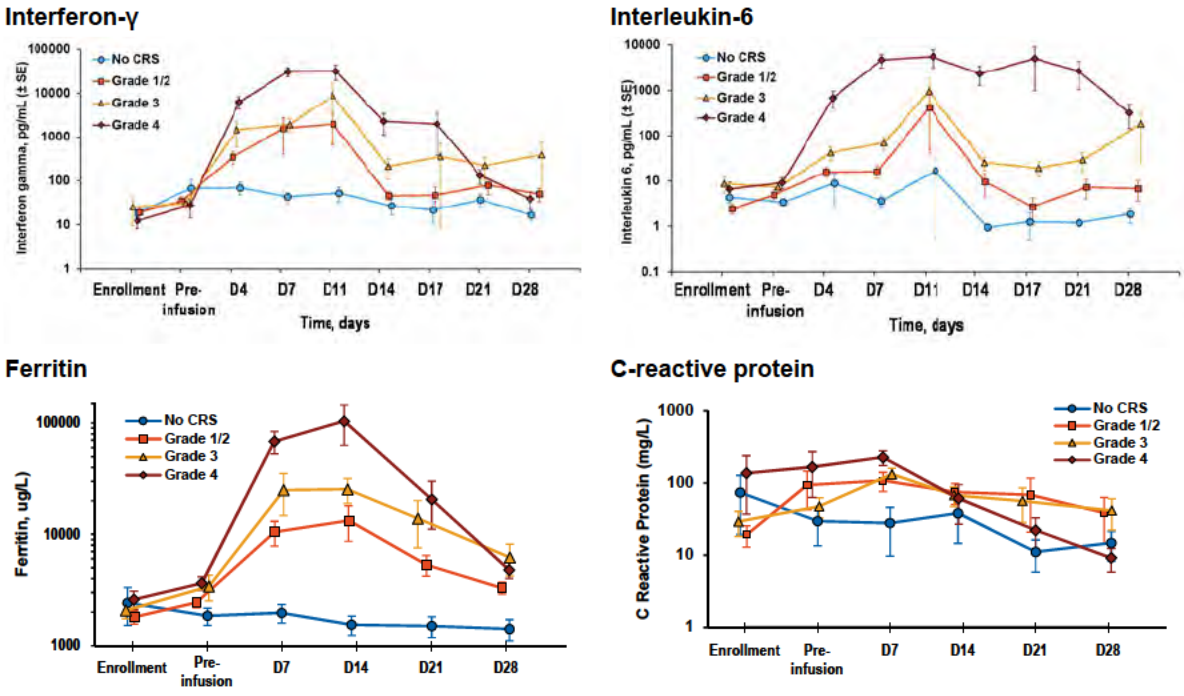
Figure 6-1 Median time to CRS onset and duration of CRS – Studies B2202 and B2205J



CRS Cytokine release syndrome

Serum cytokines such as IFN-γ and IL-6, and key inflammatory markers such as ferritin were generally elevated when patients experienced CRS. Greater elevations of these soluble factors were seen in patients with grade 3/4 CRS than in patients with grade 1/2 CRS (Figure 6-2).

Figure 6-2 Cytokine and inflammatory markers over time by CRS grade



Management of CRS included appropriate site training, stringent clinical monitoring and support, and implementation of the CRS management algorithm based on clinical presentation and severity (summarized in Table 6-14). Supportive care with O_2 and hemodynamic stabilization is the basis of first-line therapy. If there is further clinical development, patients are treated with tocilizumab, as well as additional support as required for hemodynamic and respiratory conditions. Steroid usage is considered as a third-line therapy in conjunction with additional tocilizumab.

Table 6-14 CRS management algorithm

Pre-treatment	Acetaminophen and diphenhydramine/H1 anti-histamine
Tisagenlecleucel infusion	
Prodromal syndrome: low-grade fever, fatigue, anorexia (hours to days)	
Prodromal syndrome management	Observation, rule out infection (surveillance cultures), rule out TLS Antibiotics per local guidelines (febrile neutropenia) Symptomatic support
Symptom progression: high fevers, hypoxia, mild hypotension	
First-line management	Oxygen, fluids, vasopressor support, antipyretics Monitor/manage complications of TLS
Further symptom progression (one or more of the following): Hemodynamic instability despite iv fluids and vasopressor support Worsening respiratory distress, including pulmonary infiltrates, increasing oxygen requirement including high-flow oxygen and/or need for mechanical ventilation Rapid clinical deterioration	
Second-line management	Tocilizumab: iv infusion - Patient <30 kg: 12 mg/kg iv over 1 h - Patient ≥ 30 kg: 8 mg/kg iv over 1 h (maximum dose: 800 mg) Hemodynamic and respiratory support
Lack of clinical improvement: If lack of clinical improvement despite prior management, the following management sequence is recommended. At all times, provide hemodynamic and respiratory support, and consider other diagnoses which might cause clinical deterioration (e.g. TLS, sepsis, adrenal insufficiency)	
Third-line management	If no improvement with first dose of tocilizumab within 12 to 18 hours, consider corticosteroids: - 2 mg/kg methylprednisolone as an initial dose, then 2 mg/kg/d Plan rapid taper only after hemodynamic normalization. As steroids are tapered quickly, monitor for adrenal insufficiency and need for hydrocortisone replacement If no response to steroids within 24 hours, consider second dose of tocilizumab (dosed as above)
Fourth-line management	If no response to steroids and second dose of tocilizumab within 24 hours or further clinical deterioration, consider siltuximab 11 mg/kg iv over 1 hour
Fifth-line management	In ongoing CRS despite prior therapy, consider anti-T cell therapies such as cyclophosphamide, antithymocyte globulin, or alemtuzumab

CRS Cytokine release syndrome; TLS Tumor lysis syndrome

Febrile neutropenia

Febrile neutropenia is a known consequence of both the underlying disease and the lymphodepleting chemotherapy received. Patients were considered to have febrile neutropenia if fever developed for any reason, including as the result of an infection or due to CRS.

Febrile neutropenia was reported in 35 patients (36.1%) within the 8-week period post-infusion from the Safety Pool (Table 6-12). Furthermore, 60.8% of patients experienced grade 3/4 absolute neutrophil count reductions with concurrent elevations in body temperature to >38.3°C within ±1 day (consistent with the results from Study B2101J).

In the event of febrile neutropenia, the presence of infections should be evaluated and patients managed accordingly with this possibility in mind. Febrile neutropenia should therefore be evaluated and managed per local medical standards; this includes ruling out the presence of an infection, including blood cultures and the initiation of broad-spectrum antibiotics for possible bacterial infections.

Infections

Prolonged neutropenia often occurs in the pre-engraftment phase of SCT (particularly allo-SCT) and in patients undergoing aggressive multi-agent chemotherapy. Relapsed and uncontrolled leukemia itself is also associated with prolonged neutropenia and pancytopenia. Patients with neutropenia are at increased risk of serious infection and reactivation of latent infections (bacterial, viral, and fungal) that is dependent on the severity and duration of the neutropenia. As neutropenic patients are unable to mount robust anti-microbial responses, serious infection can occur, sometimes with minimal signs and symptoms. Infections in neutropenic patients can progress rapidly, leading to hypotension and/or other life-threatening complications. Fever is associated with most serious infections, and is often the only clinical manifestation in these patients. Neutropenia can be effectively managed by early detection of neutropenic fever and prompt initiation of systemic anti-microbial therapy. However, the frequency of infections and fatality rates increase as the duration of neutropenia increases following chemotherapy or SCT (Blennow et al 2014).

The risk of infection is considered to be manageable with appropriate monitoring and prophylactic or therapeutic intervention, if required. Infections were reported in 44.3% of patients within the initial 8-week period post-infusion in the Safety Pool, with 21.6% of patients with grade 3/4 events (Table 6-15). Patients enrolled in tisagenlecleucel studies are known to have a higher risk of infection at enrollment and to have a higher risk of intercurrent illness due to neutropenia associated with ALL and prior chemotherapy, immunosuppression, lymphodepleting chemotherapy, and B-cell aplasia from the direct action of infused tisagenlecleucel.

Table 6-15 Infection-related events occurring in 2% or more of patients – Studies B2202 and B2205J

	All infused patients N=97					
	All grades		Grade 3		Grade 4	
Preferred term	n (%)		n (%)		n (%)	
Any infection	**43**	**(44.3)**	**18**	**(18.6)**	**3**	**(3.1)**
Staphylococcal infection	5	(5.2)	2	(2.1)	0	
Clostridium difficile infection	4	(4.1)	3	(3.1)	0	
Conjunctivitis	4	(4.1)	0		0	
Rhinovirus infection	4	(4.1)	0		0	
Staphylococcal bacteremia	3	(3.1)	3	(3.1)	0	
Pneumonia	3	(3.1)	2	(2.1)	0	
Candida infection	3	(3.1)	0		1	(1.0)
Clostridium difficile colitis	3	(3.1)	0		0	
Herpes simplex	2	(2.1)	1	(1.0)	0	
Human herpes virus-6 infection	2	(2.1)	1	(1.0)	0	
Oral herpes	2	(2.1)	1	(1.0)	0	
Gastroenteritis norovirus	2	(2.1)	0		0	
Nail infection	2	(2.1)	0		0	
Oral candidiasis	2	(2.1)	0		0	

The 2 additional grade 4 events not listed in this table were single cases of parainfluenza and mucormycosis

Three patients developed infections that proved to be fatal (Table 6-10).

Patients with active, uncontrolled infections should not start tisagenlecleucel therapy until the infection is controlled. Prior to tisagenlecleucel infusion, infection prophylaxis should follow local guidelines based on the degree of preceding immunosuppression.

In patients achieving complete remission following tisagenlecleucel therapy, resulting low immunoglobulin (Ig) levels can increase the risk for infection. In patients with low Ig levels, Ig replacement therapy should be administered and attention to signs and symptoms of infection should be implemented as per age and local specific guidelines.

Neurological events

Neurological events (SMQ: non-infectious encephalopathy/delirium) have been observed in patients following various types of T-cell-directed therapy. The mechanisms underlying the neurological symptoms (e.g. aphasia, tremor, seizures, confusion, and encephalopathy) remain poorly understood. It has been reported that MAS/HLH alone due to other causes can also be associated with neurotoxicity. Encephalopathy typically occurs during CRS or immediately following the resolution of CRS and is self-limiting. Tisagenlecleucel is frequently found in the cerebrospinal fluid of patients with or without neurological symptoms, suggesting that the transduced T cells may not be direct mediators of neurotoxicity (Maude et al 2014, Porter et al 2015).

Transient neurological events were reported in 40.2% of patients in the Safety Pool within 8 weeks of tisagenlecleucel infusion, with no grade 4 and no fatal events (Table 6-12). The most frequently reported events were confusional state (12.4%), encephalopathy (9.3%), and delirium (8.2%) (Table 6-16). The majority of cases appear to be self-limiting and resolve without specific intervention.

Of note, no cases of cerebral edema were reported.

Table 6-16 Neurological events within the initial 8 weeks occurring in 2 or more patients – Studies B2202 and B2205J

	All infused patients N=97				
	All grades		Grade 3		Grade 4
Preferred term	n (%)		n (%)		n (%)
Any neurological event [1]	**39**	**(40.2)**	**11**	**(11.3)**	**0**
Confusional state	12	(12.4)	0		0
Encephalopathy	9	(9.3)	4	(4.1)	0
Delirium	8	(8.2)	3	(3.1)	0
Agitation	6	(6.2)	0		0
Tremor	6	(6.2)	0		0
Irritability	5	(5.2)	0		0
Somnolence	4	(4.1)	1	(1.0)	0
Hallucination	4	(4.1)	0		0
Cognitive disorder	3	(3.1)	1	(1.0)	0
Seizure	3	(3.1)	1	(1.0)	0
Lethargy	3	(3.1)	0		0

	All infused patients N=97					
	All grades		Grade 3		Grade 4	
Preferred term	n (%)		n (%)		n (%)	
Dysphagia	2	(2.1)	2	(2.1)	0	
Depressed level of consciousness	2	(2.1)	1	(1.0)	0	
Mental status changes	2	(2.1)	1	(1.0)	0	
Muscular weakness	2	(2.1)	1	(1.0)	0	

MedDRA Medical Dictionary for Regulatory Activities; SMQ Standard MedDRA query
[1] Includes events in the non-infectious encephalopathy/delirium SMQ

Hematopoietic cytopenias lasting >28 days

Patients may continue to exhibit cytopenias for several weeks or months post-tisagenlecleucel infusion and should be managed in accordance with local treatment guidelines. Although the incidence of neutropenia and thrombocytopenia was 50% to 60% on or prior to Day 28 post-infusion, the majority of these events resolved (defined as grade ≤ 2) by Month 3. Cytopenias were typically considered to be a consequence of the lymphodepleting chemotherapy, underlying disease, prior rounds of treatment (chemotherapy, radiotherapy, and/or SCT), with possible attribution to tisagenlecleucel.

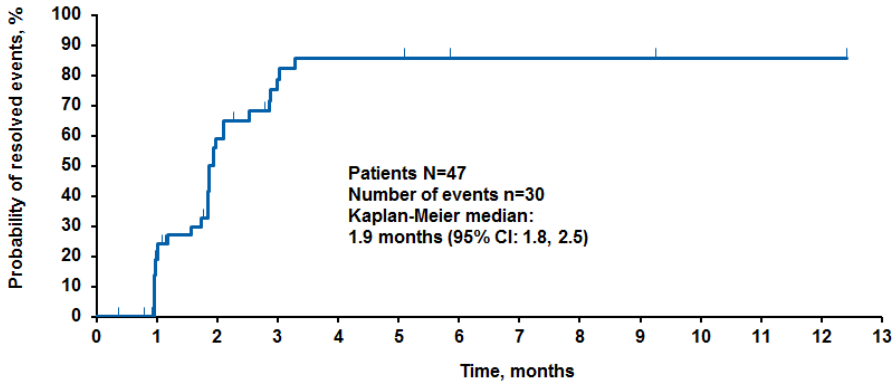
Persistent grade 3/4 cytopenias were observed beyond Day 28 post-tisagenlecleucel infusion but continued to resolve with time (Table 6-17). Recovery of the cell count for patients with grade 3/4 cytopenias is summarized in Figure 6-3 and Figure 6-4; most of the cases were resolved by the end of the second month. These cytopenias were manageable with standard clinical measures (i.e. administration of antibiotics and routine supportive care). Two fatalities were reported in patients with prolonged cytopenia: one due to a systemic fungal infection and the second tentatively attributed to encephalitis (HHV-6). Both of these patients had persistent neutropenia on trial entry.

Table 6-17 Resolution of hematopoietic cytopenias – Studies B2202 and B2205J

	All infused patients N=97					
	Day 28 [1]		By Month 3 [2]		By Month 6 [2]	
Parameter	n (%)		Patients at risk	% unresolved probability	Patients at risk	% unresolved probability
Neutrophils	59	(60.8)	15	36.0	1	2.6
WBC	58	(59.8)	15	35.3	1	2.6
Platelets	47	(48.5)	6	21.3	2	14.2
Lymphocytes	46	(47.4)	15	44.6	1	4.2
Hemoglobin	12	(12.4)	0	NE	0	NE

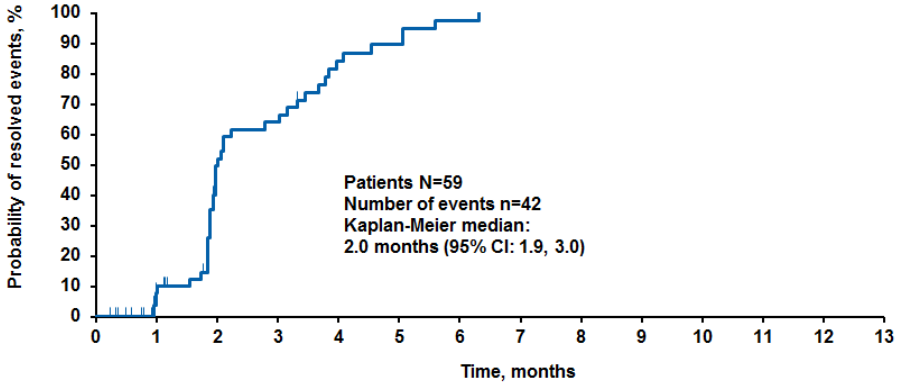
NE Not evaluable; WBC White blood cells
[1] Number of patients with last value on or prior to Day 28 indicating grade 3 or 4 cytopenia
[2] Resolution of cytopenia was defined as attaining laboratory results of grade ≤ 2

Figure 6-3 Time to resolution of grade 3/4 thrombocytopenia – Studies B2202 and B2205J



CI Confidence interval

Figure 6-4 Time to resolution of grade 3/4 neutropenia – Studies B2202 and B2205J



CI Confidence interval

Tumor lysis syndrome (TLS)

As with any therapy resulting in significant tumor cell destruction, adoptive CAR T-cell therapy can potentially lead to the release of nucleic acids, catabolites, and intracellular ions into the circulation which then manifests as TLS. Tumor lysis syndrome typically occurs in patients with large tumor burden and/or in patients with highly proliferative malignancies, particularly acute leukemia. While TLS has been observed commonly following conventional cytotoxic chemotherapy, it has also been seen in a small number of patients treated with CD19 CAR T-cells (Table 6-12). Perhaps as a result of the use of TLS prophylaxis and also the gradual rather than exponential kinetics of in vivo stimulated CD19 CAR T-cell expansion (with peak proliferation at 1-2 weeks), TLS was not a major toxicity in the initial B-cell ALL Phase-I studies, even in patients with high leukemia burdens. However, should it occur, TLS can be life threatening although it is managed by standard supportive therapy (Davila et al 2014, Lee et al 2014, Maude et al 2014).

Generation of replication-competent lentivirus (RCL)

Replication-competent lentivirus generation was monitored using a qPCR assay for vesicular stomatitis virus-G (VSV-G) and patient samples were monitored at 3, 6, and 12 months post-infusion of tisagenlecleucel and yearly thereafter. No generation of RCL was observed post-infusion.

Insertional oncogenesis

A lentiviral vector insertion site analysis was performed on tisagenlecleucel manufactured from cells of 12 patients and 2 healthy volunteers. There was no evidence for preferential integration near genes of concern, or preferential outgrowth of cells harboring integration sites of concern during cell culture in the manufacturing process, and the final product showed a high degree of polyclonality.

Other toxicities

Mild infusion reactions can be seen and are controlled by pre-medication with acetaminophen and anti-histamines. In the various studies presented, lymphodepleting chemotherapy is administered prior to tisagenlecleucel infusion. In case of febrile reactions, patients should also be evaluated for infections and appropriate treatment instigated.

Prolonged B-cell aplasia is an expected on-target toxicity of successful CD19-directed CAR T-cell therapy and acts as a useful surrogate to determine functional persistence of treatment and is observed in all responding patients. As long as modified T-cells persist in the patient, B-cell aplasia continues and results in hypogammaglobulinemia. This makes the patient more susceptible to infection; this is adequately managed with immunoglobulin replacement therapy (Maude et al 2015).

6.4 Clinical chemistry and hematology – Studies B2202 and B2205J

6.4.1 Clinical chemistry abnormalities – Studies B2202 and B2205J

New or worsened clinical chemistry abnormalities were mainly reported as grade 1/2.

The pattern and timing of acute liver enzyme elevations during tisagenlecleucel associated CRS are consistent with those previously reported in Study B2101J (Maude et al 2014, Fitzgerald et al 2017). Eighteen patients (19.8%) (2×grade 1/2 CRS, 2×grade 3 CRS, and 14×grade 4 CRS) presented with concurrent ALT/AST concentrations >3-times the upper limit of normal (ULN) and bilirubin >2×ULN and alkaline phosphatase (ALP) <2×ULN within the initial 8-week period post-tisagenlecleucel infusion. Similar criteria were not observed at any time >8 weeks post-infusion. These changes are thought to be mechanistically related to cytokine elevations associated with CRS, supported by the known effects of direct IL-6 infusion on the liver (van Gameren et al 1994).

6.4.2 Hematology abnormalities – Studies B2202 and B2205J

Hematologic laboratory abnormalities were common (Table 6-18).

Grade 3/4 laboratory hematopoietic cytopenias were considered as AESIs for tisagenlecleucel if they persisted beyond Day 28 post-infusion (see Section 6.3.2.2.3), and were considered to have resolved once a laboratory value of grade ≤ 2 was reached.

Table 6-18 Hematology laboratory abnormalities – Studies B2202 and B2205J

	All infused patients N=97	
	All grades n (%)	Grade 3/4 n (%)
WBC decreased	97 (100.0)	93 (95.9)
Hemoglobin decreased	97 (100.0)	49 (50.5)
Neutrophils decreased	95 (97.9)	93 (95.9)
Lymphocytes decreased	95 (97.9)	90 (92.8)
Platelets decreased	91 (93.8)	72 (74.2)

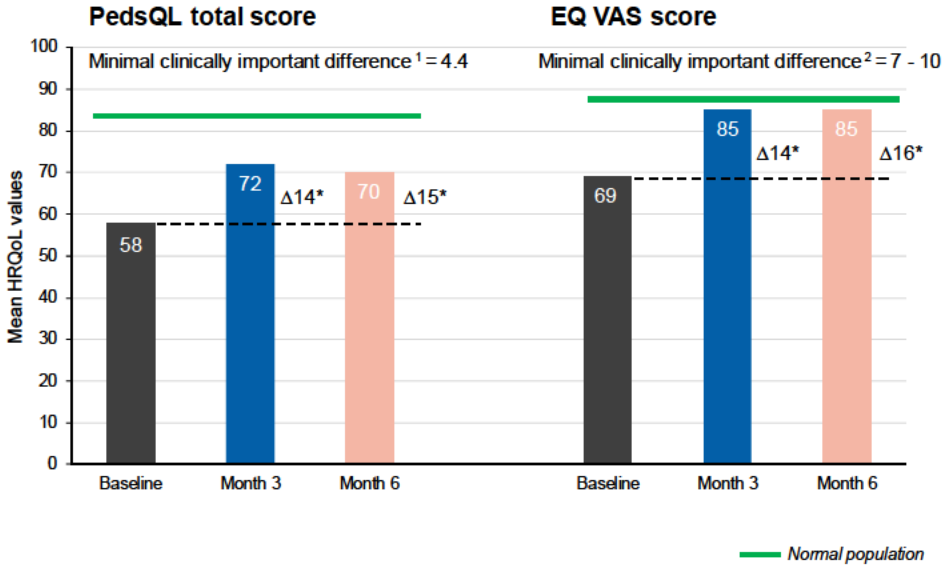
WBC White blood cells

6.5 Patient-reported outcome data – Study B2202

Patient-reported HRQoL data, analyzed with two different tools, indicated an overall improvement in HRQoL after tisagenlecleucel infusion in Study B2202. Questionnaires were completed at scheduled visits by patients aged ≥ 8 years prior to the patient interacting with the Investigator or undergoing any clinical assessments. The majority of patients who failed to respond to treatment and those who relapsed dropped out from the study and as a result their PRO data were unavailable. Results therefore correspond to patients who were responding to treatment.

- **Pediatric quality of life inventory (PedsQL) questionnaire**
  Higher scores on the PedsQL questionnaire for emotional, social, school, physical, and psychosocial health subscales were reported at Month 3 relative to baseline, indicating better HRQoL post-tisagenlecleucel infusion. This improvement in HRQoL was maintained at Month 6 (Figure 6-5).
  Mean changes from baseline in the PedsQL total score were 5.4 at Day 28 (n=32), 13.5 at Month 3 (n=30), and 15.3 at Month 6 (n=25), with a minimal clinically important difference of 4.4 for a self-report sample (Varni et al 2003).
- **EuroQol visual analogue scale (EQ VAS) questionnaire**
  Mean changes from baseline were 5.0 at Day 28 (n=32), 14.1 at Month 3 (n=28), and 15.5 at Month 6 (n=24), with estimated minimally important differences for the EQ VAS among cancer patients in the range from 7 to 10 (Figure 6-5) (Pickard et al 2007). Furthermore, while the mean EQ VAS score at baseline (69.1) was comparable to that of patients sampled from cancers of various etiologies (Pickard et al 2007), the mean scores at Month 3 (84.7) and Month 6 (84.7) were comparable to normative means of the general population (EuroQol Group 2004, Holtzer-Goor et al 2015).

Figure 6-5 Improvement in patient-reported QoL post-tisagenlecleucel infusion relative to baseline – Study B2202



EQ VAS EuroQol visual analogue scale; HRQoL Health-related quality of life; PedsQL Pediatric quality of life inventory; QoL Quality of life

* Mean change from baseline in patients who had both baseline and post-baseline scores
** Only patients aged ≥ 8 years were required to complete the assessments
[1] Varni et al 2003
[2] Pickard et al 2007

These results support improved QoL beyond the period of acute toxicities for this one-time immunocellular therapy.

6.6 Adverse events – Study B2101J

6.6.1 Frequent adverse events – Study B2101J

The nature and incidence of AEs reported in Study B2101J were similar to those reported in the Safety Pool. All patients experienced ≥ 1 AE post-tisagenlecleucel infusion. The most commonly reported events were hematologic-related events (96.4%) and CRS (89.1%) (Table 6-19).

The most frequently observed grade 3/4 AEs (occurring in ≥ 30% of patients) were: febrile neutropenia (78.2%), neutrophil count decreased (67.3%), lymphopenia (65.5%), WBC count decreased (60.0%), CRS (47.3%), platelet count decreased (47.3%), decreased appetite (36.4%), hypotension (32.7%), hemoglobin decreased (30.9%), and ALT increased (30.9%).

Table 6-19 Adverse events post-tisagenlecleucel infusion occurring in at least 30% of patients by grade – Study B2101J

	Non-CNS3 ALL patients N=55		
	All grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Number of patients with at least 1 AE	55 (100.0)	11 (20.0)	40 (72.7)

	Non-CNS3 ALL patients N=55					
	All grades n (%)		Grade 3 n (%)		Grade 4 n (%)	
Non-hematologic AEs						
Cytokine release syndrome	49	(89.1)	12	(21.8)	14	(25.5)
Aspartate aminotransferase increased	41	(74.5)	12	(21.8)	4	(7.3)
Vomiting	41	(74.5)	4	(7.3)	0	
Alanine aminotransferase increased	40	(72.7)	13	(23.6)	4	(7.3)
Headache	39	(70.9)	7	(12.7)	0	
Nausea	39	(70.9)	7	(12.7)	0	
Decreased appetite	35	(63.6)	19	(34.5)	0	
Hypotension	29	(52.7)	3	(5.5)	15	(27.3)
Diarrhoea	28	(50.9)	0		0	
Pain	25	(45.5)	6	(10.9)	0	
Tachycardia	25	(45.5)	0		1	(1.8)
Fatigue	24	(43.6)	0		0	
Chills	20	(36.4)	0		0	
Cough	20	(36.4)	0		0	
Activated partial thromboplastin time prolonged	19	(34.5)	5	(9.1)	0	
Blood creatinine increased	19	(34.5)	1	(1.8)	0	
Abdominal pain	18	(32.7)	2	(3.6)	0	
Pyrexia	18	(32.7)	1	(1.8)	0	
Hyperphosphataemia	17	(30.9)	0		0	
Hematologic AEs						
White blood cell count decreased	52	(94.5)	17	(30.9)	14	(25.5)
Neutrophil count decreased	50	(90.9)	13	(23.6)	23	(41.8)
Haemoglobin decreased	50	(90.9)	12	(21.8)	4	(7.3)
Platelet count decreased	46	(83.6)	9	(16.4)	16	(29.1)
Lymphopenia	44	(80.0)	20	(36.4)	15	(27.3)
Febrile neutropenia	43	(78.2)	35	(63.6)	8	(14.5)
Hypogammaglobulinaemia	34	(61.8)	0		0	

AE Adverse event; Non-CNS3 ALL Active CNS involvement excluded

Adverse events by total number of infusions – Study B2101J

Results of an analysis by the number of infusions (1 infusion: n=11; 2 infusions: n=28; 3 infusions: n=14; 4 infusions: n=2) showed that several of the more common AEs were reported more frequently in patients receiving a single infusion relative to those receiving 2 infusions: AST increased (100% vs. 64.3%; Δ+35.7%), pain (72.7% vs. 39.3%; Δ+33.4%), ALT increased (90.9% vs. 64.3%; Δ+26.6%), hypotension (72.7% vs. 46.4%; Δ+26.3%), headache (81.8% vs. 60.7%; Δ+21.1%), hemoglobin decreased (100% vs. 85.7%; Δ+14.3%), vomiting (90.9% vs. 78.6%; Δ+12.3%), CRS (90.9% vs. 82.1%; Δ+8.8%), and nausea (72.7% vs. 67.9%; Δ+4.8%). No notable differences were evident in AE frequency when comparing patients who had received 2 infusions with those whose dose was split into 3 separate infusions.

6.6.2 Deaths – Study B2101J

Fifteen deaths (27.3%) occurred in patients with non-CNS3 ALL (i.e. no active CNS involvement) in Study B2101J; all were attributed to disease progression. No death occurred within the initial 30 days of the first infusion. Three deaths were reported in the initial 30-day period after the last tisagenlecleucel infusion (16, 22, and 27 days, respectively post-infusion).

6.7 Deaths in ongoing adult ALL studies

In an early, ongoing Phase-II Study CTL019B2203J (UPCC-21413) (hereafter B2203J) in adult patients with r/r B-cell ALL, the initial 6 patients were infused with a single dose of tisagenlecleucel within a dose range of 1 to 5×10^8 transduced T cells. Three early deaths (between Days 5 and 15 from the last tisagenlecleucel infusion) were reported due to refractory CRS with concurrent, clinically significant infections (influenza B, pseudomonas pneumonia, and gram-negative sepsis); patients were aged 32, 56, and 63 years.

Two further deaths, on Days 10 and 16 following tisagenlecleucel infusion, were reported with a lower dose of 5×10^7 transduced T cells. These patients were aged 50 and 66 years. The CRS in these two cases was deemed not to be refractory to intervention. One case was associated with a fatal intracranial hemorrhage with concurrent grade 4 CRS and grade 4 acute respiratory distress syndrome. The second case was reported with a fatal grade 5 sepsis, pneumonia, and acidosis, with concurrent grade 4 CRS, along with a skin infection due to Gram-positive cocci, Clostridium difficile infection, and hypoxia. (Of note, adult patients with r/r ALL typically have more chemotherapy refractory disease and additional comorbidities than younger patients.)

It is important to note that these findings of refractory CRS with concurrent infection were observed early in the development program for adult ALL. They prompted the development and refinement of additional CRS risk mitigation strategies that were subsequently applied across all tisagenlecleucel trials at Penn, the Children's Hospital of Philadelphia, and Novartis, and included the following:

- Recommendations for use of anti-microbial prophylaxis at study entry and in the lymphodepleting chemotherapy period
- New pre-infusion criteria including influenza screening and delaying or not allowing infusion until infection control was established
- Not allowing infusion in the setting of accelerating leukemia following lymphodepleting chemotherapy or with a significant decline in performance status
- Patients experiencing toxicities from their preceding lymphodepleting chemotherapy were to have their infusion schedule delayed until these toxicities were resolved (to grade ≤ 1)
- Specific pulmonary toxicities warranting delay of tisagenlecleucel infusion included requirement for supplemental O_2 to maintain saturation >91% or the presence of progressive radiographic abnormalities on chest X-ray
- New cardiac arrhythmia uncontrolled with medical management or hypotension requiring vasopressor support

Further refinement to the CRS treatment algorithm was made including repeat tocilizumab dosing following suboptimal response. Patients were required to remain within close proximity of their treating physician for the initial 21 days post-infusion and every new site enrolling

patients was required to stagger enrollment for their first 3 patients by 14 days. Patients were instructed to take their temperature twice daily for the initial 14 days and caregivers were instructed to bring any patient with new fevers or associated symptoms immediately to the hospital for evaluation and consideration for admission. Finally, the dose schedule for adult patients with r/r ALL in Study B2203J was amended to a fractionated dose (10%, 30%, 60% of tisagenlecleucel transduced cells) to allow holding of the subsequent dose in case of early fever onset or other acute events. This resulted in manageable CRS with no early deaths.

6.8 Dose-safety and exposure-safety analyses

6.8.1 Dose-safety analyses

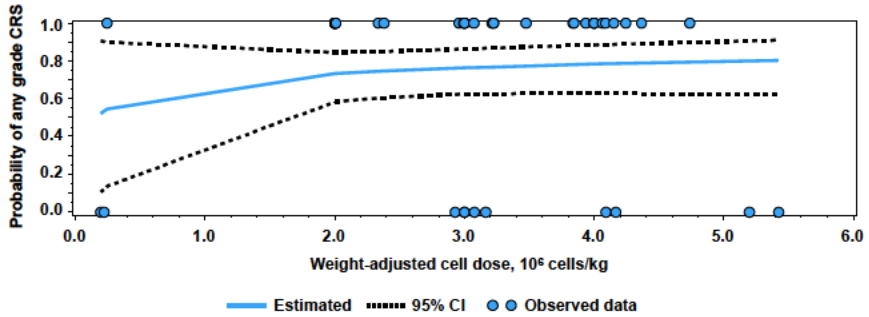
Results of dose-response logistic regression analyses in Studies B2202 and B2205J (including log-dose, study, weight category, study by log-dose, and weight by log-dose in the model) indicated there was no impact of transduced viable T cell dose on the probability of grade 3/4 CRS (Figure 6-6). As noted later, no patient died as a consequence of CRS in these trials, and CRS was manageable following the treatment algorithm provided in the protocol.

Results of further logistic regression analyses also showed the lack of an impact of dose on the probability of any grade and grade 3/4 neurological events and cytopenias.

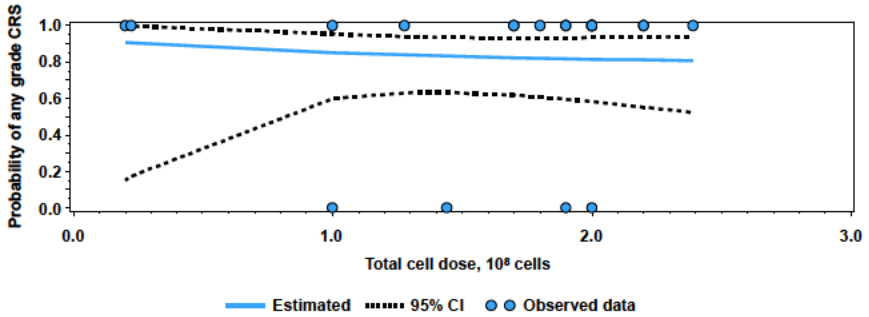
Figure 6-6 Logistic regression of CRS vs. dose, overlaid with observed data – Study B2202 (Pharmacokinetic Analysis Set)

Any grade CRS

≤ 50 kg

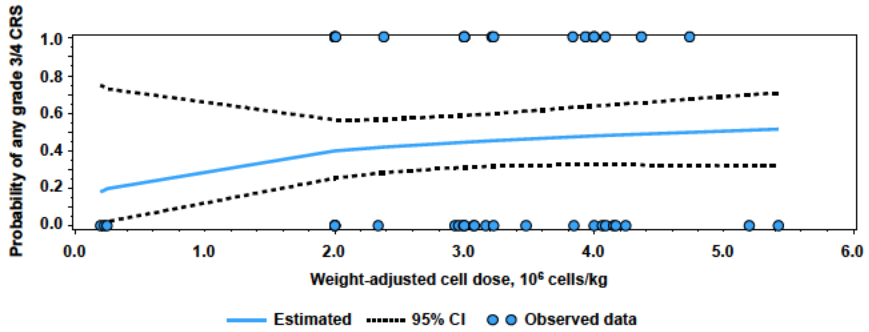


>50 kg

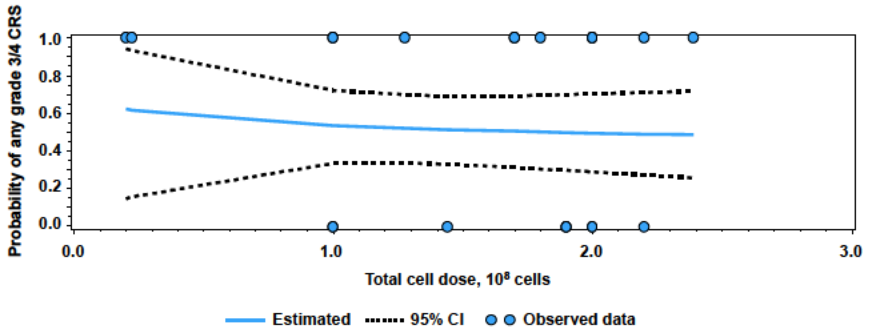


Grade 3/4 CRS

≤ 50 kg



>50 kg



CI Confidence interval; CRS Cytokine release syndrome

6.8.2 Exposure-safety analyses

Relationship between exposure and CRS grade

Results of logistic regression analyses indicated that higher tisagenlecleucel exposure (Cmax and AUC0-28d) was associated with increasing CRS grade in Studies B2202 and B2205J, and the pooled data (Table 6-20). Administration of tocilizumab did not appear to impact the cellular kinetics of tisagenlecleucel.

Table 6-20 Model estimates from logistic regression of CRS incidence vs. peripheral blood tisagenlecleucel cellular kinetic parameters – Studies B2202 and B2205J and pooled data

	Odds ratio estimate (95% CI)	
Parameter	**Any grade CRS**	**Grade 3/4 CRS**
Study B2202		
Log AUC0-28d	1.97 (1.156, 3.372)	2.58 (1.448, 4.579)
Log Cmax	1.71 (1.017, 2.862)	2.13 (1.214, 3.727)
Study B2205J		
Log AUC0-28d	2.03 (0.785, 5.248)	1.44 (0.862, 2.419)
Log Cmax	2.27 (0.872, 5.903)	1.18 (0.722, 1.933)
Pooled data		
Log AUC0-28d	2.00 (1.160, 3.453)	1.93 (1.310, 2.838)
Log Cmax	1.97 (1.142, 3.388)	1.59 (1.091, 2.302)

AUC0-28d Represents the exposure or levels of transgene attained during the initial 28 days following infusion of tisagenlecleucel; CI Confidence interval; Cmax Maximum (peak) expansion of transgene post-tisagenlecleucel infusion; CRS Cytokine release syndrome
Odds ratio is for a 2-fold increase in cellular kinetic parameter

6.9 Immunogenicity

Humoral immunogenicity was measured by determination of anti-murine CAR19 antibodies (anti-mCAR19) in serum pre- and post-infusion. In clinical Studies B2202 and B2205J, the majority of patients (84.8%) tested positive for pre-dose anti-mCAR19; however, the pre-existing antibodies were not associated with any impact on clinical response nor have an impact on the initial expansion and persistence of tisagenlecleucel. Based on limited data, lower exposure metrics (AUC0-28d, AUC0-84d, and Cmax) were seen in patients with positive post-infusion anti-mCAR19 (treatment induced) compared with patients who did not exhibit treatment-induced anti-mCAR19 antibodies (negative patients). Due to high variability with the exposure matrices data, it is difficult to conclusively attribute the difference in exposures to treatment-induced anti-mCAR19 antibody formation. Furthermore, treatment-induced anti-mCAR19 did not appear to impact response. As with any immunogenicity assay, the detection of anti-mCAR19 antibodies is highly dependent on assay sensitivity and specificity. Furthermore, the observed pre- and post-dose anti-mCAR19 may be influenced by several factors including assay specifications, sample handling, timing of sample collection, prior therapy, administration of intravenous immunoglobulin or other concomitant medications as well as the underlying disease.

7 Measures to lessen or manage adverse events post-approval

Measures to lessen or manage AEs post-approval are summarized in Table 7-1.

Table 7-1 Summary of risk management plans for post-approval setting

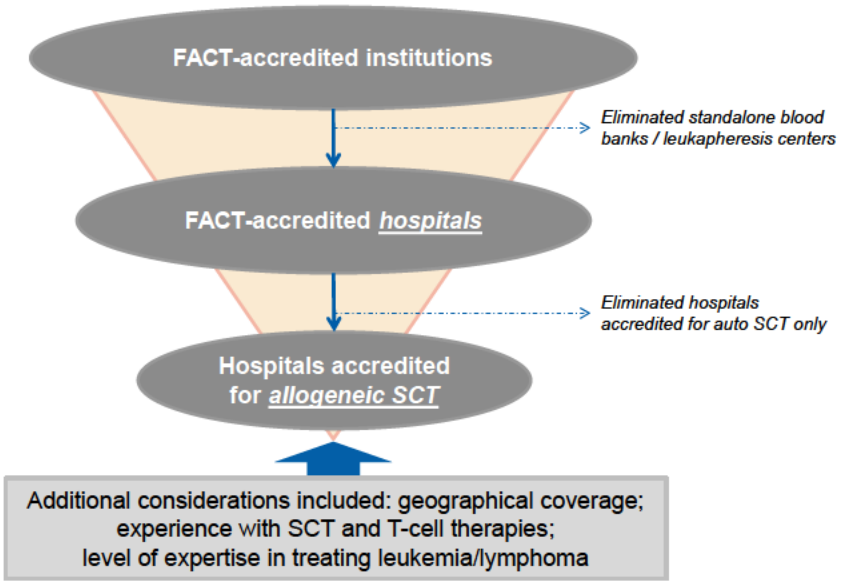
Elements	Actions
Site and prescriber onboarding	Safety training (in person and/or web-based training conducted by Novartis) - Tisagenlecleucel prescribing information - Safety management - Process and patient management
Ongoing site support and education	Dedicated tisagenlecleucel Account Managers and Field-based Medical Directors and Field Medical Liaisons Training and educational materials provided to the sites Refresher training prior to first patient infusion if needed Repeat training or additional training upon request Ongoing communication with treatment centers for therapy-related updates Medical information call center
Risk Evaluation and Mitigation Strategy	Communication plan focused on CRS and neurological events (including educational materials for healthcare providers, caregivers, and patients)
Pharmacovigilance	Full Pharmacovigilance plan submitted Patient Registry in collaboration with CIBMTR for patients treated in commercial setting

CIBMTR Center for International Blood and Marrow Transplant Research; CRS Cytokine release syndrome

To achieve the goal of safe administration and management of AEs, Novartis is committed to a staged introduction of tisagenlecleucel with select centers of excellence and medical experts in cellular therapy.

- Treatment centers able to administer tisagenlecleucel have been selected in accordance with objective criteria (Figure 7-1). Novartis is planning to launch with a network of 30-35 sites. All sites must be FACT accredited as well as being accredited to perform allo-SCT. Novartis will manage the onboarding and training of centers directly and only centers that are trained and certified will be able to collect cells for tisagenlecleucel manufacturing and subsequently prescribe and administer the product.

Figure 7-1 Selection of treatment centers with infrastructure to treat patients with tisagenlecleucel



FACT Foundation for the Accreditation of Cellular Therapy; SCT Stem-cell transplantation

A comprehensive education plan is proposed targeting individual stakeholders (e.g. transplanters, ICU staff, nurses, etc). Dedicated Novartis teams will also be available to provide ongoing support and education (Figure 7-2).

- Comprehensive training for treatment centers will cover the standards for collection, cryopreservation, and transport of cells, as well as the prescribing information, patient, and safety management for the respective clinical teams

Figure 7-2 Dedicated tisagenlecleucel Account Managers and Field Medical for ongoing support and education

The Hematology Sales Team will also play a supporting role by ensuring treatment awareness in the community (and in appropriately triaging referrals and requests)

- Educational materials will also be required for caregivers and patients. Novartis will provide this information.

Novartis will recommend that treatment be withheld for certain patients.

- As described earlier, tisagenlecleucel is an autologous cellular immunotherapy. The logistics of this personalized therapy differ from other immune therapies, and this involves a waiting time while the product is manufactured. The majority of patients will receive bridging chemotherapy (at the clinician's discretion) followed by lymphodepleting therapy prior to tisagenlecleucel infusion. Adverse events reported during this period are consistent with the known safety profiles of these agents. Due to the risks associated with tisagenlecleucel therapy, infusions should be withheld if a patient presents with any of the following conditions:
  - Unresolved serious adverse reactions from preceding chemotherapies especially pulmonary and cardiac including hypotension
  - Any active uncontrolled infection
  - Grade 2-4 acute or extensive chronic GvHD
  - Significant clinical worsening of leukemia burden following lymphodepleting chemotherapy

Finally, to ensure continued patient safety post-approval, a comprehensive monitoring plan and registry have been proposed to FDA.

- A detailed Pharmacovigilance Plan is proposed. A REMS is also proposed – the goal of which is to educate HCPs about the serious risks of CRS and neurological events by providing information on the:
  - Risk of CRS, which may be life-threatening
  - Serious clinical manifestations associated with CRS
  - Serious risk of neurological events observed in association with tisagenlecleucel
  - Timing of CRS and neurological events in relation to the tisagenlecleucel infusion
  - Management of CRS (see Table 6-14 and Table 7-2)
  - Signs and symptoms of CRS and neurological events and guidance as to when to seek immediate medical attention for patient/caregiver education

Table 7-2 CRS risk mitigation strategy

Prior to infusion	Following infusion
Efforts should be made to: - Lower and control tumor burden - Provide appropriate prophylactic and therapeutic treatment for infection - Ensure complete resolution of any existing infections	CRS management algorithm - Anti-IL-6 cytokine-directed therapies tocilizumab and siltuximab for the management of moderate or severe CRS (tocilizumab is required on site and available for administration prior to infusion)

Prior to infusion	Following infusion
Hold infusion (until resolved) if: - Unresolved SAEs from preceding chemotherapies – especially pulmonary, cardiac, or hypotension - Any active uncontrolled infection - Significant clinical worsening of leukemia burden (following lymphodepleting chemotherapy)	Patients instructed to stay within 2 hours of treatment site for at least 3 to 4 weeks after receiving treatment
Acetaminophen and diphenhydramine/ H1 anti-histamine	Patients and caregivers instructed to call oncologist or present to the Emergency Room upon appearance of signs/symptoms of high fever
Prophylaxis for complications of tumor lysis syndrome, as appropriate	Patients and caregivers instructed to carry a wallet card with safety information about CRS

CRS Cytokine release syndrome; SAE Serious adverse event

- The specific objectives of the REMS have been shared with FDA together with a timetable for the submission of assessments evaluating the effectiveness of the REMS and recommendations for improvements or changes should these be required
- A Patient Registry is planned to capture both short-term AESIs (i.e. CRS and neurological events) and long-term AESIs (i.e. secondary malignancies, monitoring for RCL, B-cell aplasia, and other delayed AEs)

8 Benefit-risk evaluation

8.1 Structured benefit-risk assessment

Compelling, consistent, and robust evidence for the clinical benefit of tisagenlecleucel in pediatric and young adult patients with r/r B-cell ALL was demonstrated in both pivotal Study B2202 and supportive Studies B2205J and B2101J (Table 8-1).

Table 8-1 Structured benefit-risk assessment

Factor Evidence	Conclusion and reasons
Analysis of condition	
r/r pediatric B-cell ALL is a rare indication Approximately 15% of pediatric patients with B-cell ALL relapse within 3 years of first-line anti-leukemia therapy Long-term survival of patients with r/r B-cell ALL is generally poor, with a median OS of 3 to 6 months Most of these patients with r/r B-cell ALL will die due to their disease	r/r B-cell ALL in pediatric and young adult patients has a poor prognosis, is generally incurable, and is a leading cause of death in pediatric oncology
Unmet medical need	
Relapsed ALL is currently treated with salvage chemotherapy, targeted antibody therapy, allogeneic SCT, or supportive care; these options are rarely curative Remission rates in r/r B-cell ALL using currently available therapies including clofarabine and blinatumomab are 20% to 39% Current regimens are associated with chronic dosing and short-term efficacy and may serve only as a bridge to SCT in patients who can achieve remission after these therapies	Majority of pediatric and young adult patients with r/r B-cell ALL relapse after treatment with current standards of care Significant unmet medical need to improve outcomes in pediatric and young adult patients with B-cell ALL whose disease has relapsed or is refractory to therapy Safe and effective new treatments are warranted

Factor Evidence	Conclusion and reasons
Clinical benefit	
Primary endpoint of Study B2202 was met. ORR within 3 months after infusion was 82.5% (95% CI: 70.9, 90.9; p<0.0001); this was clinically meaningful and statistically significant. Response rates considerably exceed those observed with clofarabine or blinatumomab (see Table 8-2). Single infusion of tisagenlecleucel represents an additional advantage compared to chronic or continued dosing with presently available treatment options in this setting All sensitivity analyses were consistent with the primary efficacy analysis demonstrating the robustness of the efficacy outcome All patients with CR/CRi had MRD-negative bone marrow. ORR with MRD-negative bone marrow was 82.5% (95% CI: 70.9, 90.9; p<0.0001). Median DoR was not reached. Event-free probability among responders was 75.4% (95% CI: 57.2, 86.7) at Month 6 and 63.8% (95% CI: 41.5, 79.4) at Months 9 and 12. Substantial improvements in QoL (measured by PRO tools in patients ≥ 8 years) were noted at 3 and 6 months post-tisagenlecleucel infusion Study B2101J has the longest follow-up of the tisagenlecleucel trials, with a maximum follow-up of 40.5 months. Median OS was 32.7 months, and the probability of survival at Month 24 was 62.6%.	Tisagenlecleucel demonstrates compelling and consistent clinical efficacy with high response rates, and deep and durable remissions, in the majority of patients without additional therapies, across three pediatric and young adult r/r B-cell ALL studies (pivotal Study B2202 and supportive Studies B2101J and B2205J) Tisagenlecleucel represents a new treatment paradigm and a major improvement in the treatment of these patients with high unmet medical need
Risks	
Safety of tisagenlecleucel is consistent across the three clinical studies in pediatric and young adult patients with B-cell ALL In the Safety Pool, AEs, SAEs, and AESIs occurred more frequently within the first 8 weeks (e.g. 82.5% grade 3/4 AEs) compared to timepoints ≥ 8 weeks (e.g. 41.3% grade 3/4 AEs) CRS is an expected on-target toxicity and the most frequent SAE associated with tisagenlecleucel therapy - CRS onset occurred within the initial 22 days post-infusion - CRS was reversible - No fatalities occurred due to refractory CRS in the pediatric and young adult B-cell ALL program - Severity of CRS correlated with high tumor burden and early onset of fever Grade 3 neurological toxicities occurred in 11.3% of patients (no grade 4); these events are associated with higher CRS grades Febrile neutropenia is an expected AE from lymphodepleting chemotherapy and tisagenlecleucel occurring in 36.1% patients within 8 weeks post-infusion. Grade 3/4 absolute neutrophil count decreases with temperatures >38.3°C within ±1 day were observed in 60.8% of patients Infections commonly occurred due to neutropenia and B-cell aplasia. Several deaths due to infection occurred prior to or shortly after the infusion; these were associated with complications of prolonged neutropenia.	Safety profile of tisagenlecleucel is well characterized; toxicity is manageable by appropriately-trained healthcare providers, and consistent across three clinical studies in pediatric and young adult patients with r/r B cell ALL Long-term risks such as RCL, secondary malignancies, or other tisagenlecleucel suspected AEs will be further established in the 15-year long-term follow-up Study A2205B
Risk management	
CRS was managed through close monitoring for onset in patients, alertness for and assertive treatment of infectious events, control of pre-infusion tumor burden, early care and intervention according to CRS management algorithm and treatment with anti-IL-6 antibodies Risk of febrile neutropenia was managed by standard practice of hospital admission, culture surveillance, antibiotics, and supportive care Neurological toxicities were generally of short duration and reversible, and were managed with supportive care and investigation for CNS infections or bleeding Other serious ADRs were managed by monitoring and appropriate supportive care	Risks will be minimized by: 1. Restricting infusions to appropriate patients with controlled leukemia and without infections immediately prior to infusion 2. Rigorous training of sites and physicians 3. Education of physicians, caregivers, and patients as detailed in the REMS which comprises a communication plan Label will provide instructions for

Factor Evidence	Conclusion and reasons
	monitoring for the onset and management of CRS, based on CRS management algorithm

ADR Adverse drug reaction; AE Adverse event; AESI Adverse event of special interest; ALL Acute lymphoblastic leukemia; CR Complete remission; CRi Complete remission with incomplete blood count recovery; CRS Cytokine release syndrome; DoR Duration of response; IL Interleukin; MRD Minimal residual disease; ORR Overall remission rate; r/r Relapsed/refractory; PRO Patient-reported outcomes; QoL Quality of life; REMS Risk Evaluation and Mitigation Strategy; SAE Serious adverse event; SCT Stem-cell transplantation

8.2 Overall benefit-risk assessment

Current multi-agent regimens serve the majority of first-line patients with ALL well with cure rates exceeding 85% (Hunger and Mullighan 2015); however, approximately 15% of children and young adult patients with ALL will relapse. Relapsed ALL is recognized as one of the leading causes of cancer death in pediatric and young adult patients (Tallen et al 2010). Although most pediatric patients with relapsed ALL will achieve a second remission, the challenge remains to maintain this remission as most patients who relapse once will subsequently relapse again and ultimately succumb to their disease (Ko et al 2010, Tallen et al 2010, Martin et al 2012).

The limited treatment options available for pediatric and young adult patients with relapsed or refractory disease fail to address the needs of this population (Table 8-2). Innovative treatment strategies based on the use of novel anti-leukemia agents are therefore urgently needed. Allogeneic SCT is a potentially curative option but eligibility is dependent upon both disease and patient characteristics and treatment is associated with significant morbidity and mortality. Tisagenlecleucel represents the first salvage therapy in this setting that may be curative and be administered as a definitive therapy as opposed to a bridge to allo-SCT.

Compelling efficacy of tisagenlecleucel in pediatric and young adult patients with r/r B-cell ALL was demonstrated in both the pivotal registration Study B2202 and two supportive trials, with high ORRs (with high rates of MRD-negative status achieved for patients in remission) and long DoRs (Table 8-2). A homogeneous treatment effect was evident across all subgroups in the pivotal study, irrespective of bone marrow burden and prior allo-SCT.

Table 8-2 Efficacy overview: comparison with available treatments for pediatric and young adult patients with r/r B-cell ALL

	Clofarabine monotherapy	Blinatumomab	Tisagenlecleucel		
	Jeha et al 2006	von Stackelberg et al 2016 [1]	B2101J	B2205J	B2202
No. of patients	61	70	55	29	68
Prior SCT	29.5%	57.1%	63.6%	58.6%	56.5%
≥ 3 prior regimens	62.3%	11.4%	89.1%	NA [2]	60.3%
ORR (CR plus CRi)	19.7%	38.6%	94.5%	69.0%	82.5% [3]
Median OS	**3.0 mo**	**7.5 mo**	**32.7 mo [4]**	**NR**	**16.6 mo [5]**
12-month OS	20%	38%	80.6%	61.7%	79.2%
Early mortality (≤ 30 days)	24.6%	7.1%	5.5%	6.8%	2.9%

	Clofarabine monotherapy	Blinatumomab	Tisagenlecleucel		
	Jeha et al 2006	von Stackelberg et al 2016 [1]	B2101J	B2205J	B2202

CR Complete remission; CRi Complete remission with incomplete blood count recovery; NR Not reached; ORR Overall remission rate; OS Overall survival; SCT Stem-cell transplantation

[1] Based on all 70 patients who received the recommended dose in Phase-I or -II studies
[2] Median prior of lines of therapy: 3 (range: 1-9)
[3] Based on the 63 patients in the Efficacy Analysis Set
[4] Survival probability beyond 24 months should be interpreted with caution as only 11 patients had follow-up >24 months
[5] Median value should be interpreted with caution as approximately 84% of patients were still alive (and therefore censored in the analysis) at the time of the data cut-off, and only 2 patients were at risk at timepoints beyond 16 months

Safety of tisagenlecleucel is predictable and toxicity is manageable following established protocols and with appropriately-trained healthcare providers. Treatment is associated with significant toxicity in the initial 8 weeks post-tisagenlecleucel infusion, especially in patients with high disease burden; however, AEs can be minimized with the application of specific algorithms/guidelines at centers with appropriate training in tisagenlecleucel safety management. Furthermore, a return to near-normal QoL was observed (for patients in remission) in the pivotal trial. A REMS is proposed – the goal of which is to educate HCPs about the serious risks of CRS and neurological events.

- The majority of patients develop CRS (with the severity correlating with disease burden). This can be effectively managed with a detailed treatment algorithm that was established in the 3 trials forming this program. Key elements of this algorithm include an improved CRS grading scale and the administration of anti-cytokine therapy if mandated. Cytokine release syndrome is limited to the first 6 weeks post-infusion. No fatal cases of refractory CRS have been observed in pediatric and young adult patients with B-cell ALL to date.
- Neurological events are transient and typically occur within the initial 30 days post-tisagenlecleucel infusion
- Other AEs are well characterized and are manageable with supportive care
- Patients with pre-existing and prolonged neutropenia post-tisagenlecleucel infusion may be at increased risk for severe or fatal infections
- Five deaths were reported in Studies B2202 and B2205J post-tisagenlecleucel infusion that were not attributed to the underlying disease (these deaths were due to cerebral hemorrhage in the setting of DIC, embolic stroke from an intracardiac mucormycotic mass, and 3 deaths secondary to infection)

While acknowledging the limitations and difficulties of cross-trial comparisons, pooled data from Studies B2202 and B2205J compared favorably with clofarabine monotherapy and blinatumomab with regard to early mortality ($\leq$ 30 days), while a number of differences appeared to be evident in the respective incidences of important clinical events (Table 8-3).

Table 8-3 Safety overview: comparison with available treatments for pediatric and young adult patients with r/r B-cell ALL

	Clofarabine	Blinatumomab		Tisagenlecleucel
Early mortality (≤ 30 days) [1]	**25%**	**7%**		**4%**
Adverse events [2]		**≥ 45 kg**	**<45 kg**	
Cytokine release syndrome grade 3/4	NA	3% [3]	4% [3]	44% [3]
Neurological events grade 3/4	NA	17%		11%
Infusion reactions	NA	34%	44%	0%
Infections by high-level group term				
Infections – pathogen unspecified	NA [4]	45%	42%	42%
Viral infectious disorders		13%	9%	29%
Bacterial infectious disorders		19%	11%	22%
Fungal infectious disorders		14%	7%	11%

CRS Cytokine release syndrome; CTCAE Common Terminology Criteria for Adverse Events; NA Not available; Penn University of Pennsylvania

[1] Based on Jeha et al (2006) for clofarabine and von Stackelberg et al (2016) for blinatumomab
[2] Based on clofarabine USPI (revised 10/2016) and blinatumomab USPI (revised 5/2017)
[3] CRS grading based on CTCAE for blinatumomab and based on Penn grading for tisagenlecleucel
[4] Infections reported in USPI based on preferred terms rather than high-level group terms. Events occurring in ≥ 10% of patients include: sepsis including septic shock (17%), catheter-related infection (12%), oral candidiasis (11%), herpes simplex (10%), and pneumonia (10%)

In conclusion, tisagenlecleucel offers pediatric and young adult patients with r/r B-cell ALL a clinically important benefit in terms of high remission rates, long DoRs, and improved survival rates without additional therapy. These results compare favorably to the poor outcomes reported with other current treatment modalities. The safety profile of tisagenlecleucel is manageable when administered by appropriately-trained site personnel although patients may require ICU-level care for the management of severe CRS. Overall, tisagenlecleucel is associated with a positive benefit-risk profile and represents a new treatment paradigm for these patients with high unmet medical need.

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