Chimeric Antigen Receptor T-Cell Therapy for B-Cell Cancers: Effectiveness and Value

Public Meeting – March 2, 2018

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

WIFI: NILE

PW: 5108747582

Welcome and Introduction

Why are we here today?

- Few treatment options for patients
  - Less than 1/3 of pediatric leukemia patients with relapsed disease survive five years
  - Five-year disease-free survival in relapsed non-Hodgkin's lymphoma is 10-20%
- CAR-T therapy represents a new therapeutic approach offering the possibility of better outcomes for patients and families who have run out of treatment options

Welcome and Introduction

Why are we here today?

- New paradigm-shifting treatments raise important questions about how to interpret the short-term evidence available at launch

- Expensive new treatments are entering the health system at a time when increasing health care costs are affecting families, access to affordable insurance, state and federal budgets

Welcome and Introduction

Why are we here today?

- Public discussion of the evidence on effectiveness and value to help get it right for patients now and in the future
  - How strong is the evidence on benefits and harms and what does it suggest about which patients will benefit the most?
  - How should the available evidence guide pricing and coverage policies today?
  - What future approaches to drug development, pricing, and payment would support innovation and improve access while ensuring affordability?
  - How can future research capture what matters most to patients, families, and health systems?

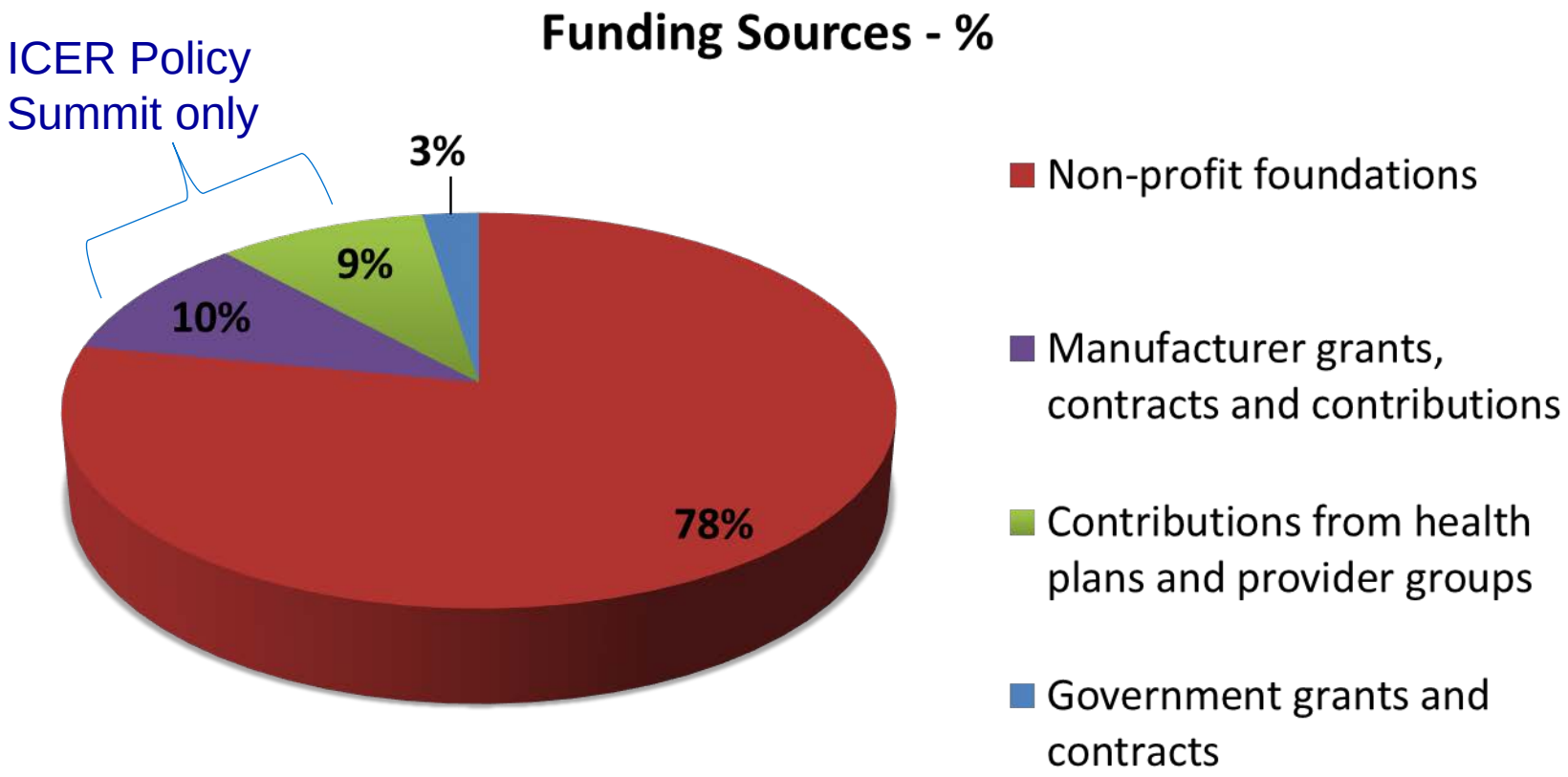
Welcome and Introduction

- California Technology Assessment Forum (CTAF)

- The Institute for Clinical and Economic Review (ICER)

Sources of Funding, 2018

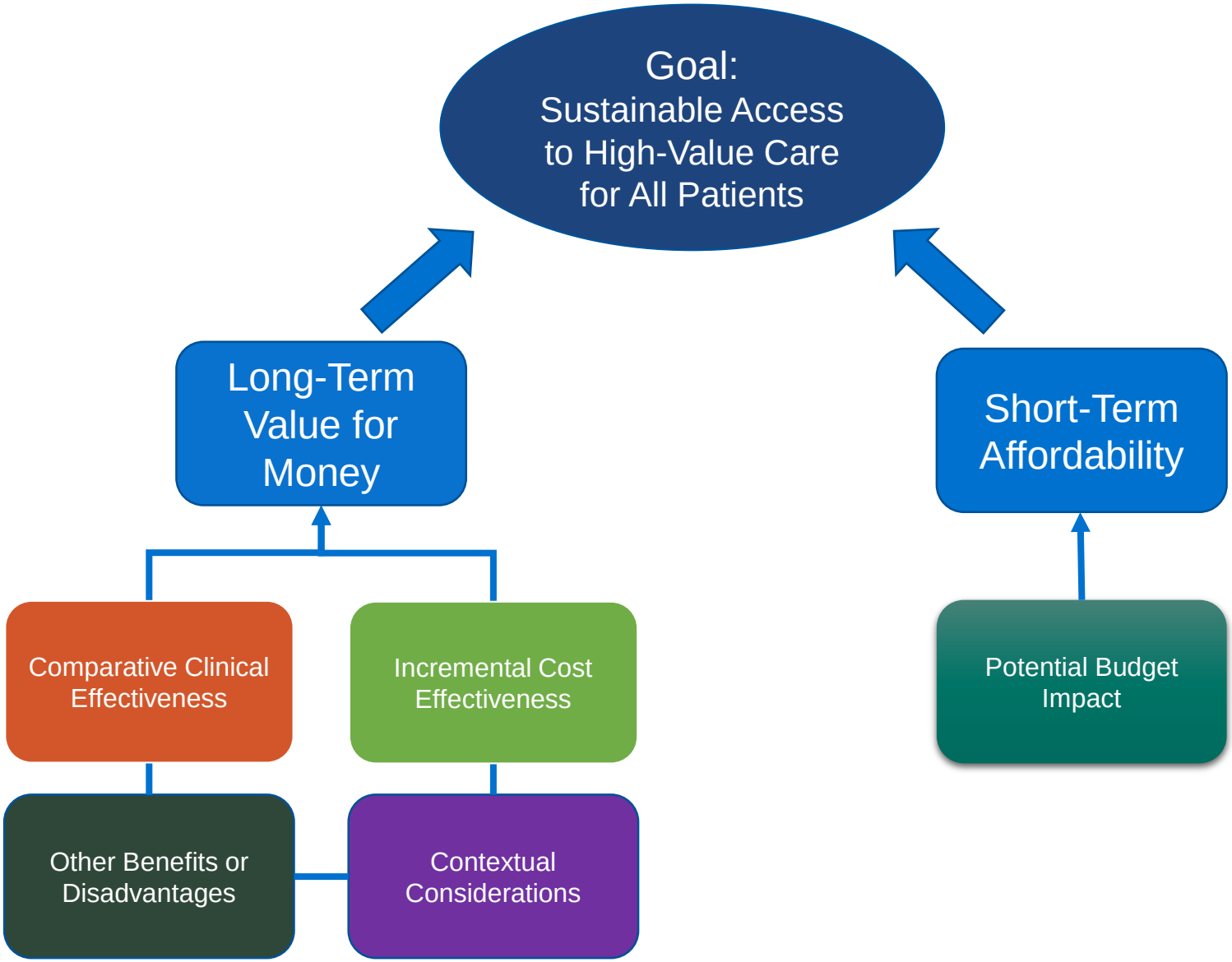
ICER Policy Summit only



Welcome and Introduction

How was the ICER report on CAR-T therapies developed?

- Scoping with guidance from patient groups, clinical experts, and other stakeholders
- Evidence analysis (ICER/UCSF) and cost-effectiveness modeling (CU)
- Public comment and revision
- Expert report reviewers
  - Charalambos (Babis) Andreadis, MD, MCSE
  - Peter Bach, MD, MAPP
  - Michelle Hermiston, MD, PhD
  - Stephen Palmer, MSc
  - Vinay Prasad, MD, MPH
- How is the evidence report structured to support CTAF voting and policy discussion?


Goal:
Sustainable Access to High-Value Care for All Patients
Long-Term Value for Money
Short-Term Affordability
Comparative Clinical Effectiveness
Incremental Cost Effectiveness
Potential Budget Impact
Other Benefits or Disadvantages
Contextual Considerations

Agenda

10:00am:	Welcome and Opening Remarks
10:15 am:	Presentation of the Evidence **Evidence Review**: Jeffrey Tice, MD **Cost Effectiveness**: Melanie Whittington, PhD
11:15 pm:	Manufacturer Comments and Discussion
11:45 am:	Public Comments and Discussion
12:15 pm:	Lunch
1:00 pm:	CTAF Deliberation and Votes
2:15 pm:	Policy Roundtable
3:30 pm:	Reflections and Wrap Up
4:00 pm:	Meeting Adjourned

Meeting materials available at: https://icer-review.org/topic/car-t/

Evidence Review

Jeffrey A. Tice, MD

Judith M. E. Walsh, MD, MPH

University of California, San Francisco

ICER

INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Key Review Team Members

Ifeoma Otuonye, MPH, Institute for Clinical and Economic Review

Aqsa Mugal, BA, Institute for Clinical and Economic Review

Disclosures:

We have no conflicts of interest relevant to this report.

Background

- Approximately 15% of children with B-cell acute lymphoblastic leukemia (B-ALL) are not cured with initial therapy and have a poor prognosis
- Aggressive B-cell non-Hodgkin's lymphomas (NHLs) including diffuse large-B-cell lymphoma (DLBCL), transformed follicular lymphoma (TFL), and primary mediastinal B-cell lymphoma (PMBCL) also have a poor prognosis if not cured following 1st and 2nd line therapy

Chimeric Antigen Receptor T-Cell Therapy

- Insert a new gene into the patient's own T-cells
  - Novel protein with an extracellular antibody fragment
  - When the antibody binds to its target:
    - T-cell activation to attack the target
    - T-cell stimulated to replicate itself
- Two CAR-T therapies today target CD19, a protein expressed by B-lymphocytes
- Potential cure: patients up to 4 years post infusion with no recurrence and no other treatment
- Median survival without CAR-T: 3 to 6 months

Unique Features of CAR-T Therapy

- Several weeks to manufacture
- Given as a single infusion
- Side effects:
  - Cytokine release syndrome (CRS): fever, hypotension, respiratory distress
  - Neurotoxicity: encephalopathy, headache, aphasia, tremors
  - Prolonged B-cell aplasia: deficits in antibodies requiring IV immunoglobulin (IVIG) therapy to prevent or treat infections

Scope of the Review

- B-ALL, ages 0-25 years, refractory or in second or greater relapse
  - Tisagenlecleucel (Kymriah™, Novartis): 3 trials
- Aggressive B-cell lymphoma in adults, refractory or in second or greater relapse
  - Axicabtagene ciloleucel (Yescarta™, Kite/Gilead): 2 trials
  - Tisagenlecleucel (Kymriah): 2 trials

Limitations of the Evidence

- Single-arm trials
  - Precludes MA, NMA
  - Selection bias in any comparison
- Small trials
  - Wide confidence intervals
- Limited follow-up time (< 2 years)
  - Uncertainty in long term follow-up
- Evolving techniques
  - Improving yields, better management of side effects

Insights Gained from Discussions with Patients

- **Hope**: CAR-T represents a potential cure
- **Fear**: of the unknown
- **Uncertainty**: will the remission endure?
- **Costs**: both of treatment and non-medical costs
- **Outcome that matters most**: long-term survival
- **Side effects**: less than anticipated; less than what they had been through already

Relapsed or Refractory Pediatric B-cell ALL

Comparators with Similar Indications

- Kymriah: B-ALL ages 0-25 that is refractory or in second or later relapse
- Clofarabine: B-ALL ages 1-21 that is refractory or in second or later relapse
- Blinatumomab: B-ALL any age that is refractory or in relapse

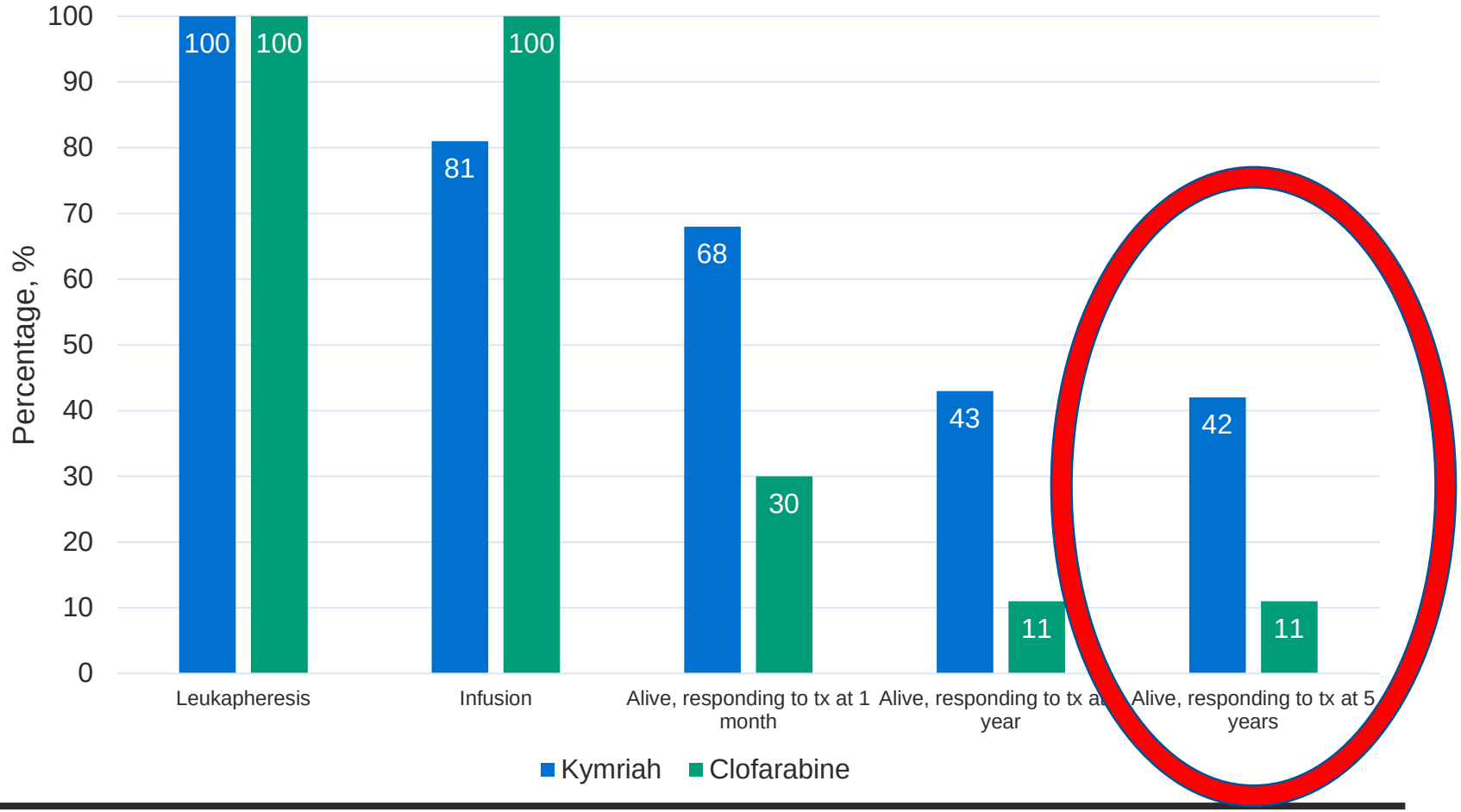
Key Clinical Trials - Characteristics

Therapy	N	F/U (months)	Age (years)	Prior Tx, median	SCT
Kymriah B2101J	55	18.6	11	4	72%
Kymriah B2205J	29	8.8	12	3	59%
Kymriah B2202/ELIANA	75	13.1	11	3	61%
Clofarabine 1	61	NR	12	3	30%
Clofarabine 2	25	NR	14	2	16%
Blinatumomab 1	70	23.8	8	2	57%
Blinatumomab 2	40	NR	9	2	53%

Key Clinical Trials – Key Outcomes

Therapy	Overall Remission Rate	Overall Survival at 12 months
Kymriah	57-73%	62-81%
Clofarabine	20-44%	20-35%
Blinatumomab	39-63%	38%

Summary of Kymriah and Clofarabine for Relapsed/Refractory B-cell ALL



Harms: Key Adverse Events in the Package Insert for Kymriah (n=68)

Adverse Reaction	Any Grade	Grade 3 or 4
Cytokine Release Syndrome	79%	49%
Neurotoxicity	65%	18%
Acute Kidney Injury	22%	13%
Infection, unknown pathogen	41%	16%
Viral Infection	26%	18%
Bacterial Infection	19%	13%
Fungal Infection	13%	7%

CRS median duration 8 days, range 1-56.
Neurotoxicity: 75% resolve within 12 days

Relapsed or Refractory Adult B-cell Lymphomas

Comparators with Similar Indications

- Yescarta (axicabtagene ciloleucel): adult patients with relapsed or refractory large B-cell lymphoma after 2 or more lines of systemic therapy
- Kymriah (tisagenlecleucel): FDA indication pending
- Chemoimmunotherapy regimens in SCHOLAR-1 trial: R-DHAP; R-ICE, etc.

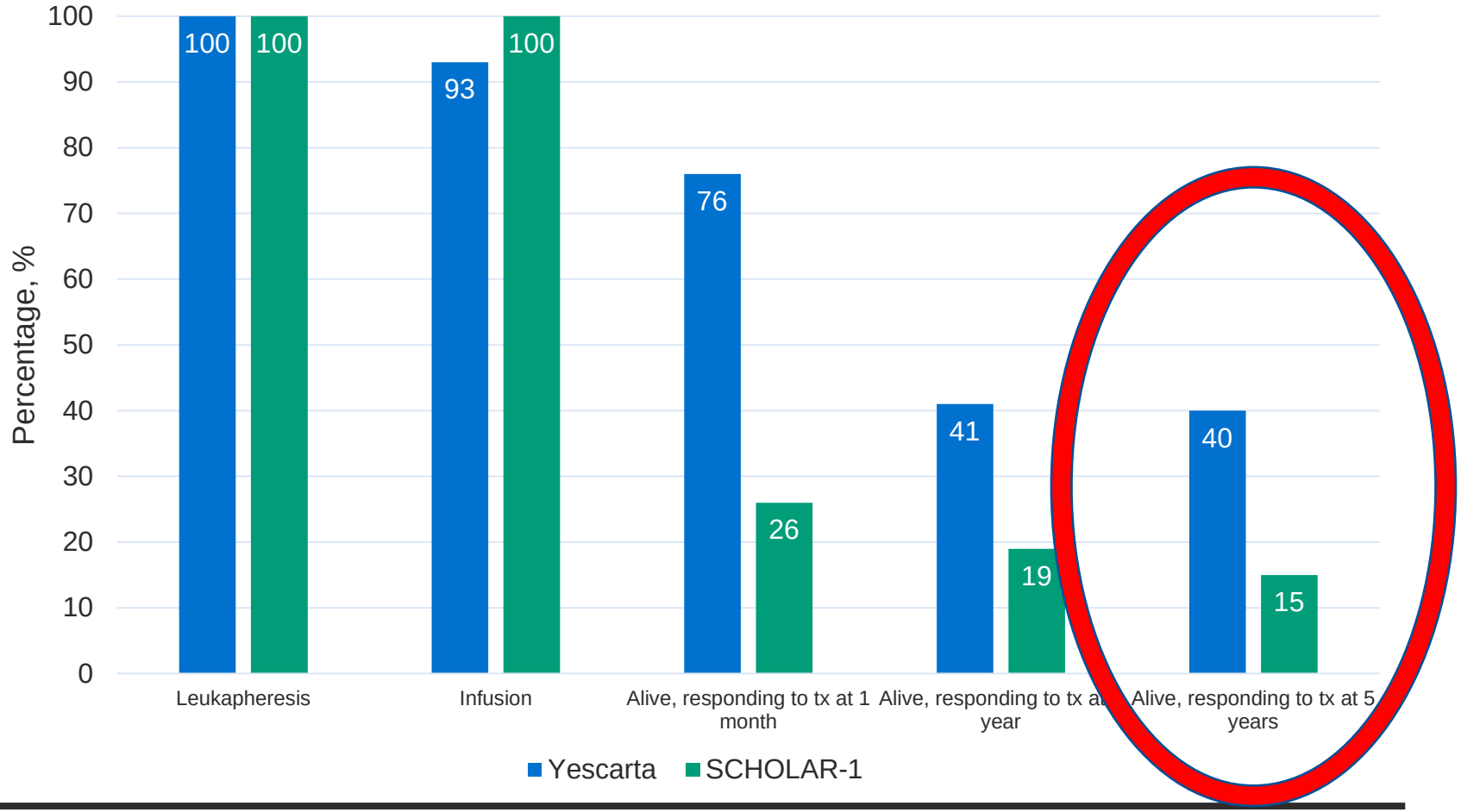
Key Clinical Trials - Characteristics

Therapy	N	F/U (months)	Age (years)	Prior Tx, median	SCT
Yescarta NCT00924326	22	NR	58	4	23%
Yescarta ZUMA-1	101	15.4	58	3	21%
Kymriah JULIET	99	NR	56	3	47%
Kymriah NCT02030834	28	28.6	57	4	35%
SCHOLAR-1	636	NR, >24	55	2	22%

Key Clinical Trials – Key Outcomes

Therapy	Complete Remission Rate	Overall Survival at 6 Months
Yescarta NCT00924326	55%	NR
Yescarta ZUMA-1	54%	80%
Kymriah JULIET	40%	NR
Kymriah NCT02030834	57%	NR
SCHOLAR-1	7%	55%

Summary of Yescarta and SCHOLAR-1 for Relapsed/Refractory B-cell Lymphoma



Harms: Key Adverse Events in the ZUMA-1 Trial for Yescarta (n=101), JULIET Trial for Kymriah (n=99)

Adverse Reaction	Yescarta Grade 3/4	Kymriah Grade 3/4
Cytokine Release Syndrome*	13%	23%
Neurotoxicity	31%	12%
Renal Insufficiency	5%	NR
Infections	NR	20%
Infection, unknown pathogen	16%	NR
Viral Infection	4%	NR
Bacterial Infection	9%	NR
Fungal Infection	NR	NR

*Different grading scale for Yescarta and Kymriah
CRS median duration 7 days, range 2-58.
Neurotoxicity median duration 12 days

Potential Other Benefits, Disadvantages and Contextual Considerations

- Novel mechanism of action
- Indicated for patients with an otherwise very limited life expectancy
- Limited to centers of excellence, which may limit access for some patients
- Considerable uncertainty in comparisons to other therapies
  - Lack of controls
  - Small n
  - Short follow-up

Summary

Controversies and Uncertainties

- Limited follow-up
  - Whether any of these treatments are “cures” is unknown
  - Long term cure rates unknown
  - Long term harms unknown
- Comparative effectiveness uncertainty
  - No head-to-head trials: potential selection bias
    - Different age distributions, prior therapies including SCT, rates of primary refractory patients, % blasts in marrow, etc.
  - Secular trends in supportive care may impact outcomes when comparing to older trials (clofarabine, SCHOLAR-1)

Public Comments Received

- New data: publications and presentations available after the draft report released
- Limited evidence: too early to review
- Uncertainty too great: should be rated “I: Insufficient”
- Evidence is substantial, rating should be “A”
- Add RIALTO data for blinatumomab
- Blinatumomab is not an appropriate comparator
- The appropriate sequencing of CAR-T therapy with other therapies is uncertain

Summary: Kymriah for Pediatric B-ALL

- Complete remission, disease-free survival, and overall survival substantially higher than comparators
- Harms comparable or better
- Thus, the existing data suggest substantial net health benefit compared with alternatives. However, given the considerable uncertainty in comparative effectiveness estimates, the true benefit may be smaller: B+ rating

Summary: Yescarta for Adult Aggressive B-Cell Lymphoma

- Complete remission, and overall survival substantially higher than comparators
- Harms comparable or better
- Thus, the existing data suggest substantial net health benefit compared with alternatives. However, given the considerable uncertainty in comparative effectiveness estimates, the true benefit may be smaller: B+ rating

Summary: Kymriah for Adult Aggressive B-Cell Lymphoma

- Complete remission rate is substantially higher than comparators
- Harms comparable or better
- Thus, the existing data suggest substantial net health benefit compared with alternatives. However, given the considerable uncertainty in comparative effectiveness estimates, the true benefit may be smaller: B+ rating

Summary: Yescarta versus Kymriah for Adult B-Cell Lymphoma

- No head-to-head studies
- Benefits may favor Yescarta, but may reflect differences in patient populations as well as chance in small trials
- Harms appear similar
- I: the evidence is insufficient to judge whether one of the CAR-T therapies is superior to the other

Long-Term Cost Effectiveness

Melanie D. Whittington, PhD
University of Colorado Anschutz Medical Campus

ICER
INSTITUTE FOR CLINICAL AND ECONOMIC REVIEW

Key Team Members

Jonathan D. Campbell, PhD, University of Colorado

R. Brett McQueen, PhD, University of Colorado

Varun Kumar, MBBS, MPH, MSc, Institute for Clinical and Economic Review

Rick Chapman, PhD, Institute for Clinical and Economic Review

Chong Kim, MPH, University of Colorado

Mausam Patidar, MS, University of Colorado

Disclosures:

Financial support was provided to the University of Colorado from the Institute for Clinical and Economic Review.

University of Colorado researchers have no conflicts to disclose defined as more than $10,000 in healthcare company stock or more than $5,000 in honoraria or consultancies relevant to this report during the previous year from health care manufacturers or insurers.

Objective

- To estimate the long-term cost effectiveness of CAR-T therapies for the treatment of B-cell malignancies.

Modeled Cohorts

- B-ALL: Patients ages 0-25 years old with B-ALL in refractory or second or later relapse
  - Intervention: tisagenlecleucel (Kymriah)
  - Comparator: 2 cycles of clofarabine monotherapy

B-ALL	Value
Median age	11.5 years
Percent female	45%
Average weight (kg)	43.0

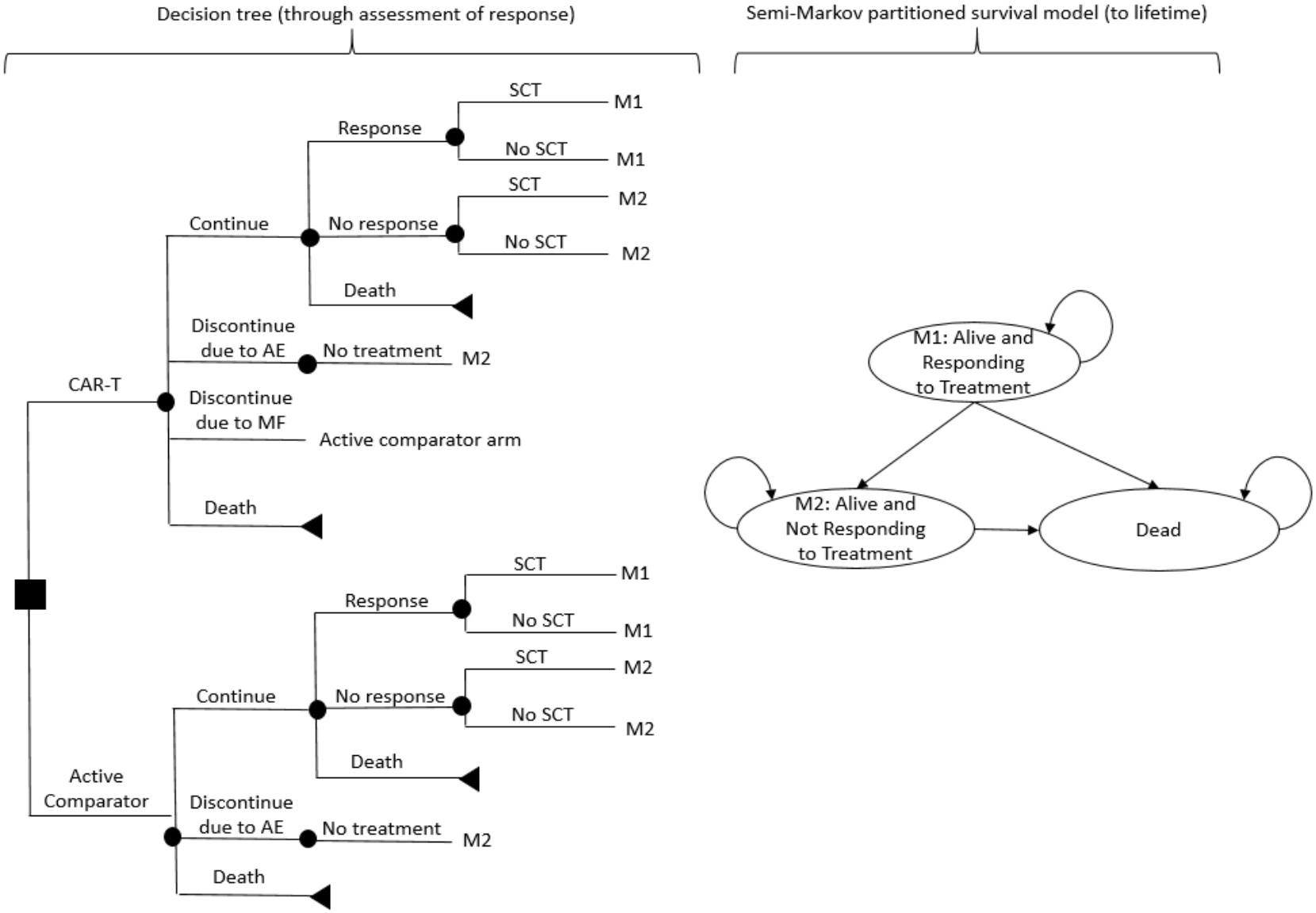
- B-cell Lymphoma: Adult patients with relapsed or refractory B-cell lymphoma after two or more lines of systemic therapy
  - Intervention: axicabtagene ciloleucel (Yescarta)
  - Comparator: chemotherapies from SCHOLAR-1, R-DHAP for cost

B-cell Lymphoma	Value
Median age	58.0 years
Percent female	32%
Average weight (kg)	82.8

Methods Overview

- Model: Decision tree and semi-Markov partitioned-survival model
- Setting: United States
- Perspective: Payer
- Time Horizon: Lifetime
- Discount Rate: 3% per year
- Outcomes:
  - Life years
  - Quality-adjusted life years
  - Incremental cost-effectiveness ratios

Model Schematic



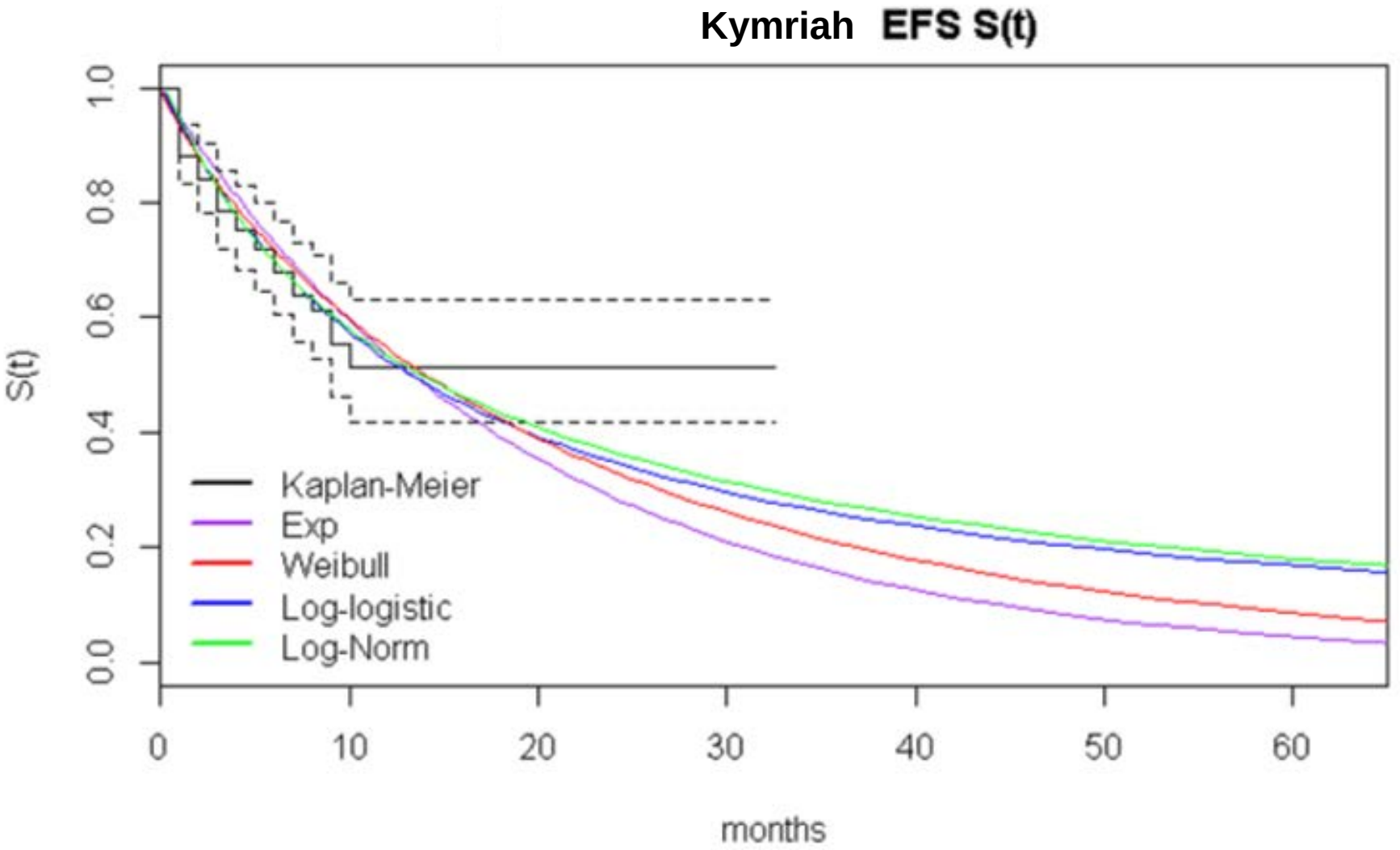
Key Assumptions

- People alive and responding to treatment at 5 years are considered long-term survivors.
- Any person alive but not responding to treatment transitioned to death by the end of year 5.
- After year 5, long-term survivors experience a mortality risk consistent with all-cause mortality rates, after adjustments for excess mortality.
- The cost of a hospitalization for treatment administration included the per diem cost for hospital days and the costs of therapies administered during the hospitalization.
  - Costs before CAR-T infusion were assumed to be administered on an outpatient basis.
- Payment for Kymriah was for responders at 1 month.
- Payment for Yescarta was at infusion.

Model Inputs: Clinical and Economic

- Clinical
  - Response to treatment
  - Survival curves
  - Stem cell transplantation
  - Adverse events
- Utilities
  - Health state utilities
  - Treatment disutilities
  - Adverse event disutilities
- Economic
  - Treatment acquisition costs
  - Hospital mark-up
  - Health care utilization costs
  - Adverse event costs

Long-Term Survival



*NR refers to not reached

Base-Case Results: Discounted Outcomes

	B-ALL		B-cell Lymphoma	
Outcome	**Kymriah**	**Clofarabine**	**Yescarta**	**Chemotherapy**
LONG-TERM SURVIVORS	**42.6%**	**10.8%**	**39.9%**	**14.8%**
Life Years (alive and responding to treatment)	9.84	2.09	6.92	2.91
Life Years (alive and not responding to treatment)	0.51	0.34	0.43	0.32
TOTAL LIFE YEARS	**10.34**	**2.43**	**7.35**	**3.23**
QALYs (alive and responding to treatment)	8.95	1.90	5.74	2.42
QALYs (alive and not responding to treatment)	0.33	0.20	0.13	0.06
TOTAL QALYs	**9.28**	**2.10**	**5.87**	**2.48**

QALY: quality-adjusted life year

Base-Case Results: Discounted Lifetime Costs

	B-ALL		B-cell Lymphoma	
Cost Category	**Kymriah**	**Clofarabine**	**Yescarta**	**Chemotherapy**
CAR-T Treatment	$405,490	$0	$438,284	$0
Chemotherapy Treatment	$15,309	$163,686	$0	$40,142
Palliative Chemotherapy Treatment	$2,648	$3,973	$3,748	$6,103
Pre-Treatment	$2,979	$0	$4,585	$0
Stem Cell Transplantation	$47,744	$64,648	$13,345	$62,094
Adverse Event Costs*	$33,534	$0	$16,029	$7,046
Administration/Monitoring	$111,548	$93,032	$44,165	$1,045
Future Healthcare	$45,901	$9,069	$95,223	$36,286
End of Life	$1,602	$2,848	$1,547	$2,169
TOTAL COSTS	**$666,754**	**$337,256**	**$616,927**	**$154,884**

Base-Case Results: Incremental Findings

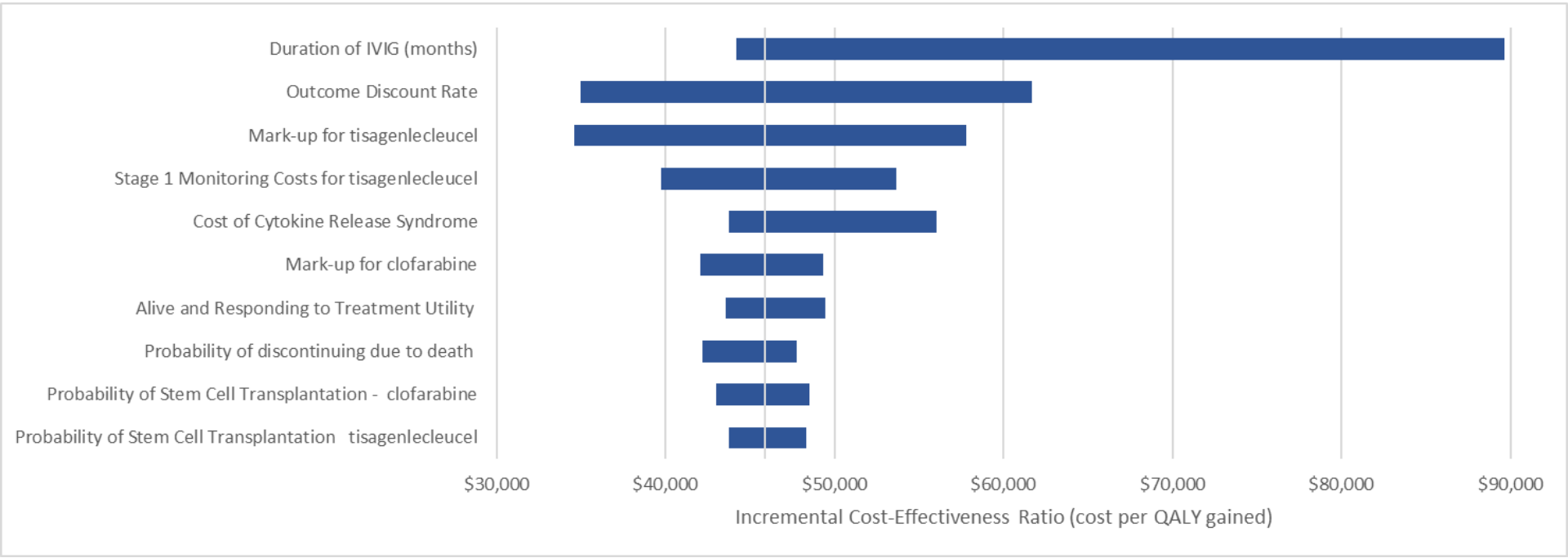
B-ALL	Incremental Costs	Incremental LYs	Incremental QALYs	Incremental CE Ratio per LY	Incremental CE Ratio per QALY
Kymriah vs. Clofarabine	$329,498	7.91	7.18	**$41,642**	**$45,871**
B-cell Lymphoma	**Incremental Costs**	**Incremental LYs**	**Incremental QALYs**	**Incremental CE Ratio per LY**	**Incremental CE Ratio per QALY**
Yescarta vs. Chemotherapy	$462,043	4.12	3.40	**$112,168**	**$136,078**

CE: cost-effectiveness, LY: life year, QALY: quality-adjusted life year

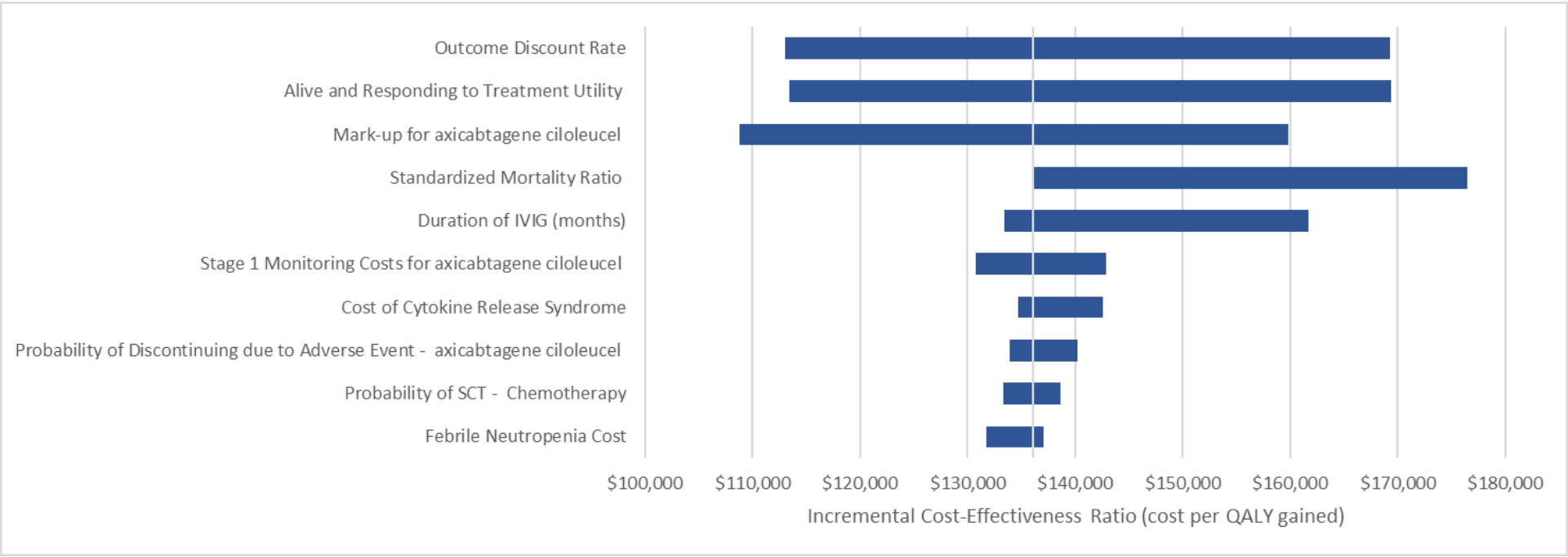
Sensitivity and Scenario Analyses

- One-way sensitivity analysis
- Probabilistic sensitivity analysis
- Alternate time horizons
- Alternate survival assumption

One-Way Sensitivity Analysis Results: Kymriah vs. Clofarabine



One-Way Sensitivity Analysis Results: Yescarta vs. Chemotherapy

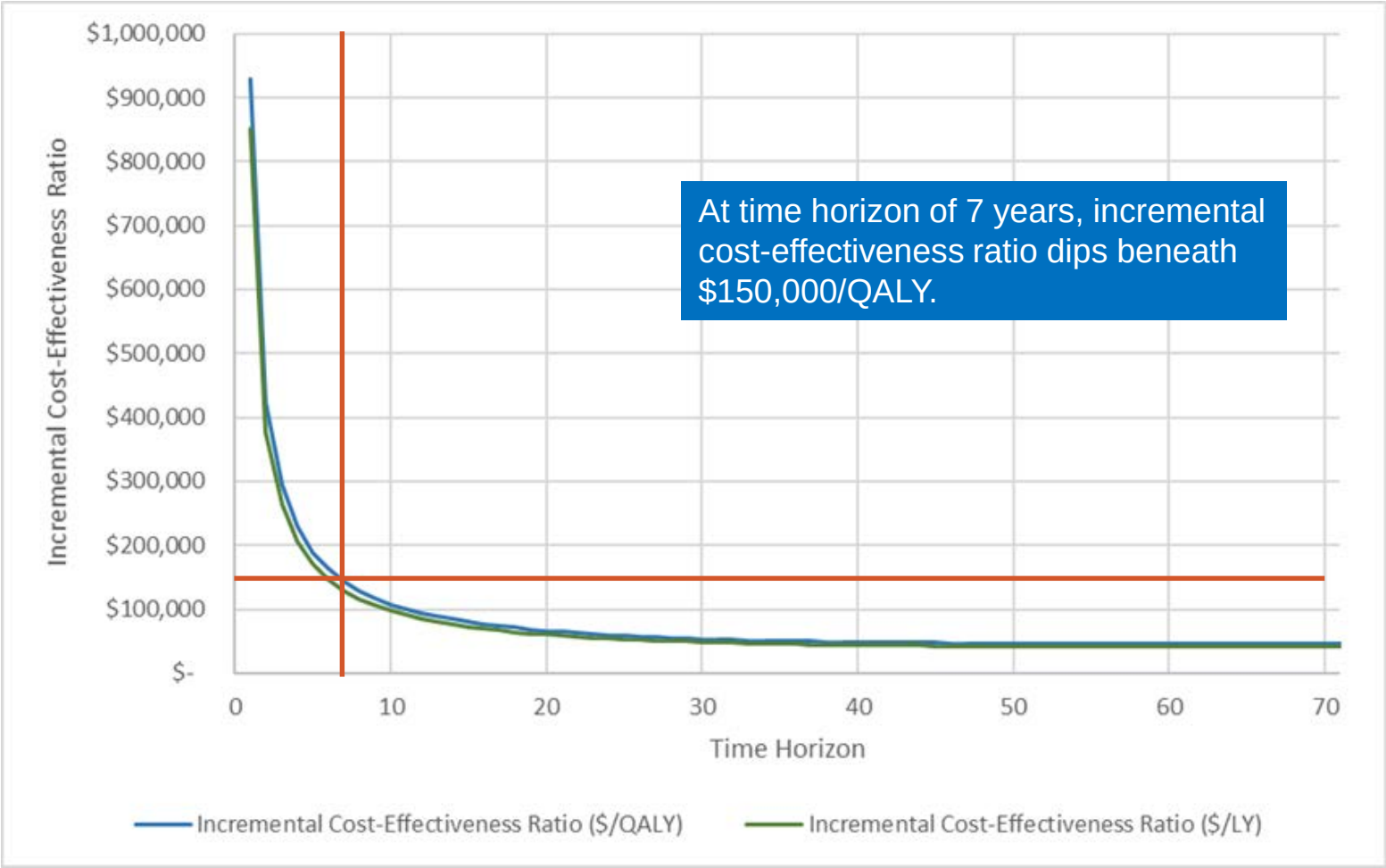


Probabilistic Sensitivity Analysis Results

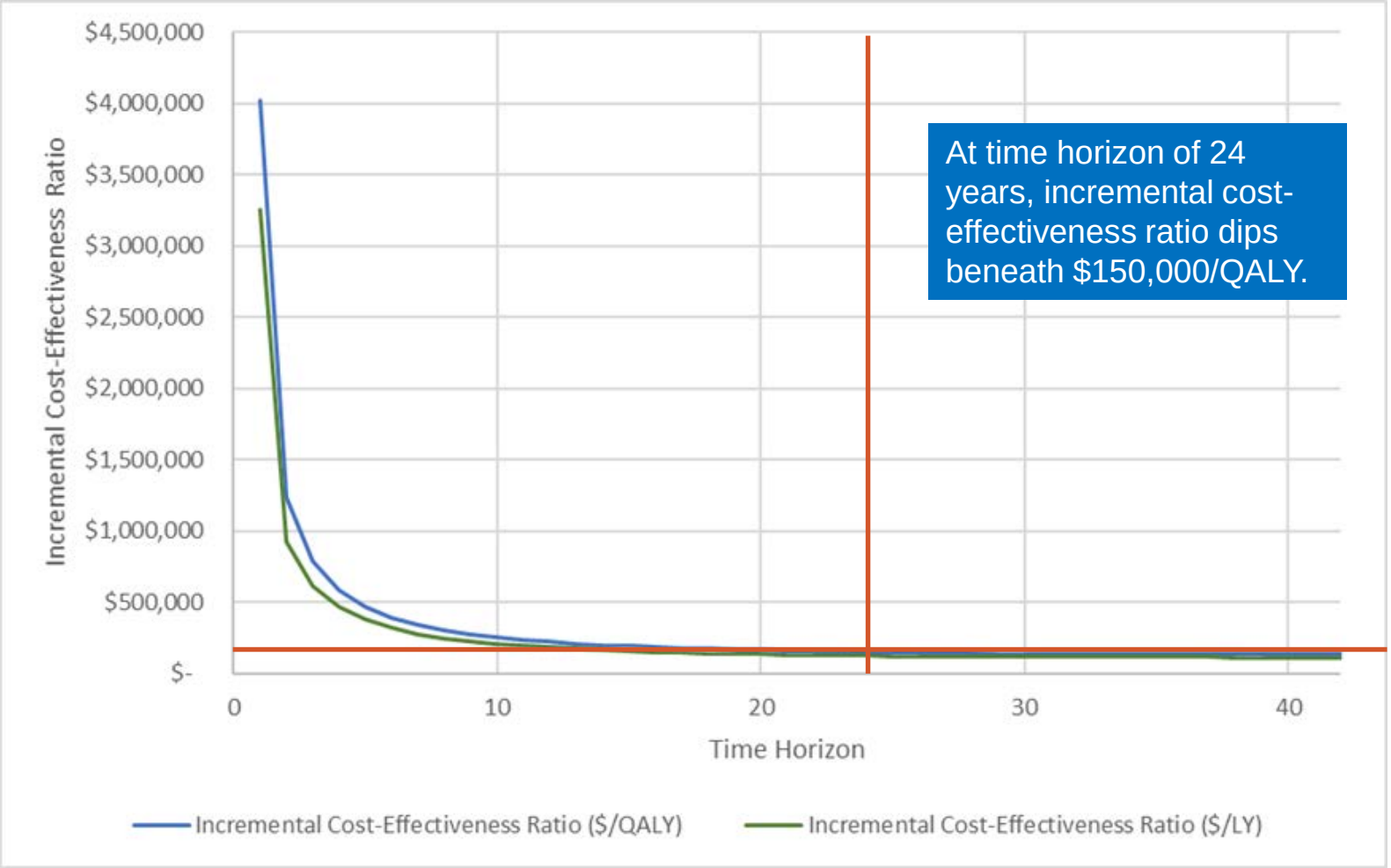
	Cost-Effective at $50,000 per QALY	Cost-Effective at $100,000 per QALY	Cost-Effective at $150,000 per QALY
Kymriah vs. Clofarabine (B-ALL)	70.6%	100.0%	100.0%
Yescarta vs. Chemotherapy (B-cell Lymphoma)	0.0%	3.0%	70.8%

Uncertainty in survival curve parameters and cost of the treatments were not included.

Alternate Time Horizon: Kymriah vs. Clofarabine (B-ALL)



Alternate Time Horizon: Yescarta vs. Chemotherapy



Alternate Survival Assumption: Standard Parametric Model

Incremental Comparison	Base-Case Survival Extrapolation ($/QALY)	Scenario Survival Extrapolation ($/QALY)
Kymriah vs. Clofarabine (B-ALL)	$45,871	$77,511
Yescarta vs. Chemotherapy (B-cell Lymphoma)	$136,078	$259,378

QALY: quality-adjusted life year

Limitations

- Limited comparative evidence (i.e., single-arm data only)
- Follow-up on progression-free survival and overall survival is limited
- Uncertainty around survival forecasting was not quantified through sensitivity analyses, but was explored through scenario analyses
- Mechanisms for payment of CAR-T therapies are still largely unknown (bundled payment, hospital mark-up)

Conclusions

- CAR-T therapies likely provide large gains in quality-adjusted and overall survival over alternative therapies
- With evidence available at this time, CAR-T therapies seem to be priced in alignment with their clinical benefits over a lifetime time horizon
  - The incremental cost-effectiveness ratio for Kymriah compared to clofarabine falls beneath $150,000 per QALY in B-cell ALL
  - The deterministic incremental cost-effectiveness ratio for Yescarta compared to chemotherapy falls beneath $150,000 per QALY gained in B-cell lymphoma
- The findings are sensitive to the time horizon and long-term benefit forecasting of the therapies

Public Comments Received

- Additional scenario analyses to account for uncertainty in long-term survival
- Clofarabine administered on an inpatient basis
- IVIG duration for an upper bound of a lifetime in the sensitivity analyses
- Stem cell transplantation for both responders and non-responders
- Updated unit cost for hospital day for each B-cell malignancy
- Disaggregated treatment costs into types of treatment (CAR-T, chemotherapy, palliative chemotherapy)

Supplemental Slides

Treatment Regimens: B-ALL

B-ALL	Regimen	Notes	Source
Kymriah	≤ 50 kg: 0.2 to 5.0×106 transduced viable T cells/kg >50 kg: 0.1 to 2.5×108 transduced viable T cells		Study B2202
Clofarabine	52mg/m^2 intravenously over 2 hours daily for 5 days, every 4 weeks, median of 2 cycles		Jeha et al., 2006
Bridging chemotherapy	Cytarabine 500mg/m2 IV for 2 days a week, 2 weeks total and methotrexate 1g/m2 IV for 1 day a week, 2 weeks total	CAR-T treatments only; 85.3% received bridging chemotherapy; duration assumed for one month	Study B2202 and Assumption
Lymphocyte depleting chemotherapy	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) OR 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)	CAR-T treatments only; 94.1% of patients received the first option and 1.5% received the second option	Study B2202
Tocilizumab	< 30 kg: 12 mg/kg intravenously over 1 hour ≥ 30 kg: 8 mg/kg intravenously over 1 hour (maximum dose 800 mg)	For the management of cytokine release syndrome	Kymriah package insert
Intravenous immunoglobulin	0.5 g/kg every 4 weeks for 11.4 months	For the management of B-cell aplasia which occurred in all CAR-T responders	Maude et al., 2017

Treatment Regimens: B-Cell Lymphoma

B-cell Lymphoma	Regimen	Notes	Source
Yescarta	2 x 10^6 CAR-T cells/kg		Locke et al., 2017
Chemotherapy (R-DHAP)	Dexamethasone 40 mg on days 1-4 + cytarabine 2 g/m^2 every 12h for 2 doses on day 2 + cisplatin 100 mg/m^2 on day 3; every 21 days for 3 cycles AND rituximab 375 mg/m^2 weekly for 4 weeks starting on day 1 of first cycle		Hernandez-Ilizaliturri et al., 2016
Bridging chemotherapy	None	No bridging chemotherapy used with Yescarta™	Locke et al., 2017
Lymphocyte depleting chemotherapy	Fludarabine (30 mg/m^2 IV daily for 3 days) and cyclophosphamide (500 mg/m^2 IV daily for 3 days)	CAR-T treatments only	Locke et al., 2017
Tocilizumab	8 mg/kg intravenously over 1 hour	For the management of cytokine release syndrome	Yescarta package insert
Intravenous immunoglobulin	0.5 g/kg every 4 weeks for 11.4 months	For the management of B-cell aplasia	Maude et al., 2017

Model Inputs: Response to Treatment

B-ALL	Kymriah	Clofarabine
Percent Achieving Response	84.4%	30.0%
Percent Dead Before Assessment of Response	7.4%	25.0%
Percent Achieving No Response	8.2%	45.0%
B-cell Lymphoma	**Yescarta**	**Chemotherapy**
Percent Achieving Response	82.0%	26.0%
Percent Dead Before Assessment of Response	0.0%	0.0%
Percent Achieving No Response	18.0%	74.0%

The denominator is the number of people who received a CAR-T infusion for CAR-T therapies and the number of people who initiated the chemotherapy regimen for comparator therapies.

Model Inputs: Kaplan-Meier Curves

B-ALL	Kymriah	Clofarabine
Event-Free Survival	Pooled event-free survival curve for Study B2202, B2205J, and B2101J	No published progression-free survival curve; therefore, the progression-free survival curve was derived from available overall survival data for clofarabine, through assuming a proportional relationship from the Kymriah™ curve.
Overall Survival	Pooled overall survival curve for Study B2202, B2205J, and B2101J	Figure 1, Overall Survival of Patients Receiving Clofarabine in Jeha et al., 2006

Model Inputs: Kaplan-Meier Curves

B-cell Lymphoma	Yescarta	Chemotherapy
Progression-Free Survival	Progression-free survival curve (Figure 2B in Neelapu et al., 2017) for ZUMA-1	No published progression-free survival curve; therefore, the progression-free survival curve was derived from available overall survival data for SCHOLAR-1 chemotherapies, through assuming a proportional relationship from a published progression-free survival and overall survival curve for R-DHAP in the same disease state.
Overall Survival	Overall survival curve (Figure 2C in Neelapu et al., 2017) for ZUMA-1	Figure 3A in SCHOLAR-1

Model Inputs: Stem Cell Transplantation

B-ALL	Kymriah*	Clofarabine
Percent That Receive Transplantation	10.5%; (16/152)	14.8%; (9/61)
B-Cell Lymphoma	**Yescarta***	**Chemotherapy**
Percent That Receive Transplantation	2.97%; (3/101)	29.9%; (180/603)

*Denominator is the number of patients that received a CAR-T infusion regardless of response status

Model Inputs: Grade 3 or 4 Adverse Events

Adverse Event	Kymriah (B-ALL)	Clofarabine	Yescarta	Chemotherapy
Abdominal Pain	3%	7%	1%	N/R
Acute Kidney Injury	13%	N/R	N/R	N/R
B-Cell Aplasia/ Hypogammaglobulinemia*	43%	N/R	15%	6.6%
Cytokine Release Syndrome	49%	N/R	13%	N/R
Decreased Appetite	15%	12%	2%	N/R
Delirium	4%	N/R	6%	N/R
Diarrhea	1%	12%	4%	N/R
Encephalopathy	10%	N/R	29%	N/R
Epistaxis	N/R	13%	N/R	N/R
Fatigue	0%	5%	3%	9%
Febrile Neutropenia	37%	54%	36%	23%
Headache	3%	5%	1%	N/R
Hypotension	22%	19%	15%	N/R
Hypoxia	18%	N/R	11%	N/R
Infections	35%	77%	23%	9%
Nausea	3%	15%	0%	8%
Pain in Extremity	1%	5%	2%	N/R
Petechiae	N/R	6%	N/R	N/R
Pyrexia	15%	14%	N/R	N/R
Tachycardia	4%	5%	2%	N/R
Vomiting	1%	9%	1%	7%

N/R: Not reported

*Any grade, not just grades 3 or 4

Model Inputs: Health State Utilities

B-ALL	Utility	Source
Alive and Not Responding to Treatment	0.75	Kelly et al., 2015
Alive and Responding to Treatment (i.e. progression-free or event-free survival)	0.91	Kelly et al., 2015
Long-Term Survivor-Alive, Responding to Treatment after 5 Years (i.e. progression-free or event-free survival)	0.91	Kelly et al., 2015
B-cell Lymphoma	**Utility**	**Source**
Alive and Not Responding to Treatment	0.39	Chen et al., 2017
Alive and Responding to Treatment (i.e. progression-free or event-free survival)	0.83	Chen et al., 2017
Long-Term Survivor-Alive, Responding to Treatment after 5 Years (i.e. progression-free or event-free survival)	0.83	Chen et al., 2017

Model Inputs: Disutilities

Health State	Disutility/Utility	Source	Notes
Chemotherapy	-0.42	Sung et al., 2003	Applied for duration of treatment. Applies to pre-CAR-T treatment chemotherapies as well.
Stem cell transplantation	-0.57	Sung et al., 2003	Applied for duration of Stage 1 and includes all decrements due to adverse events.
B-cell aplasia	-0.00	Hettle et al., 2017	Evidence did not suggest a reduction in quality of life.
Cytokine release syndrome	0.00 (UTILITY)	Hettle et al., 2017	For any grade 3 or 4 occurrence; duration equated to the median duration of ICU stay due to cytokine release syndrome (8 days).

Model Inputs: Hospital Mark-Up

- For pediatric B-ALL, the hospital mark-up for drugs administered in the CAR-T and comparator arms was price+76%.
  - The 76% was calculated by averaging the expected hospital mark-up for Medicaid (ASP+0%, no mark-up) and commercial insurance for academic/tertiary hospitals (ASP+152%).
  - We assumed all pediatric ALL patients would be treated in academic/tertiary settings.
- For adult B-cell lymphoma, the hospital mark-up for drugs administered in the CAR-T arm was price+76%.
  - The 76% was calculated by averaging the inpatient hospital mark-up for Medicare (ASP+0%, no mark-up) and commercial insurance for academic/tertiary hospitals (ASP+152%). All administrations were assumed to happen in the academic/tertiary hospital inpatient setting.
- For the adult B-cell lymphoma comparator chemotherapy arm, the hospital mark-up was price+48%.
  - The 48% was calculated by averaging the outpatient mark-up for Medicare (ASP+6%) and mark-up for commercial insurers.
  - We assumed half of commercial patients would receive chemotherapy in academic/tertiary settings and half would receive treatment in community settings (ASP+152% for hospital administration and ASP+28% for community administration).
- Mark-ups were capped at $100,000.

Model Inputs: Treatment Acquisition Costs

B-ALL	Unit	Price per Unit*	Price per Unit with Estimated Mark-Up
Kymriah	0.2 to 5.0 × 10^6 CAR-T cells/kg	$475,000†	$575,000
Clofarabine	1mg/1ml	$150	$264
Methotrexate	1mg/1ml	$0.05	$0.09
Fludarabine	1mg/1ml	$2.10	$3.70
Cyclophosphamide	1mg/1ml	$0.42	$0.74
Cytarabine	1mg/1ml	$0.01	$0.02
Etoposide	1mg/1ml	$0.05	$0.09
Tocilizumab	1mg/1ml	$4.37	$7.69
Intravenous Immunoglobulin	1mg/1ml	$0.08	$0.14

*Price as of October 8th, 2017; average sales price for all products except CAR-T

†Represents the total, not unit, wholesale acquisition costs of CAR-T therapy

Model Inputs: Treatment Acquisition Costs

B-cell Lymphoma	Unit	Price per Unit*	Price per Unit with Estimated Mark-Up
Yescarta	2 x 10^6 CAR-T cells/kg	$373,000†	$473,000
Dexamethasone	1mg	$0.33	$0.49
Cytarabine	1mg/1ml	$0.01	$0.01
Cisplatin	1mg/1ml	$0.21	$0.31
Rituximab	1mg/1ml	$8.48	$12.55
Fludarabine	1mg/1ml	$2.10	$3.70
Cyclophosphamide	1mg/1ml	$0.42	$0.74
Tocilizumab	1mg/1ml	$4.37	$7.69
Intravenous immunoglobulin	1mg/1ml	$0.08	$0.14

*Price as of October 8th, 2017; average sales price for all products except CAR-T

†Represents the total, not unit, wholesale acquisition costs of CAR-T therapy

Model Inputs: Health Care Utilization

Cost Parameter	Value	Source
Cost per Hospital day (pediatric)	$4,049	HCUP Statistical Brief #132
Cost per Hospital day (adult)	$3,037	HCUP Statistical Brief #125
Cost per day in ICU	$5,296	Dasta et al., 2005
Office Visit	$74	Physicians' Fee and Coding Guide (HCPCS code 99213)
Leukapheresis (Yescarta only)	$1,093	Physicians' Fee and Coding Guide (HCPCS code 36511)
Intravenous Treatment Administration (first hour)	$140	Physicians' Fee and Coding Guide (HCPCS code 96413)
Intravenous Treatment Administration (each additional hour)	$29	Physicians' Fee and Coding Guide (HCPCS code 96415)
Intravenous Treatment Administration (each additional sequence/drug)	$66	Physicians' Fee and Coding Guide (HCPCS code 96417)
Hematology Panel	$11	Physicians' Fee and Coding Guide (HCPCS code 82025)
Liver Function Test	$8	Physicians' Fee and Coding Guide (HCPCS code 80076)

Discounted Lifetime Costs for Subsets of Cohort

B-ALL	All Costs	CAR-T Treatment Costs	Other Costs
Kymriah + no CRS or B-cell aplasia	$765,846	$575,000	$190,846
Kymriah + CRS and B-cell aplasia	$854,966	$575,000	$279,966
Kymriah + CRS and B-cell aplasia + SCT	$1,373,791	$575,000	$798,791
B-cell Lymphoma	**All Costs**	**CAR-T Treatment Costs**	**Other Costs**
Yescarta + no CRS or B-cell aplasia	$633,523	$473,000	$160,523
Yescarta+ CRS and B-cell aplasia	$755,740	$473,000	$282,740
Yescarta + CRS and B-cell aplasia + SCT	$1,240,626	$473,000	$767,626

Manufacturer Public Comments and Discussion

Manufacturer Public Comments and Discussion

Name	Title	Company
Anna Purdum, PharmD, MS	Senior Director, Health Economics and Outcomes Research	Kite Pharma/Gilead
Richard T. Maziarz, MD	Professor of Medicine	Oregon Health and Sciences University. **Note**: Dr. Maziarz is speaking on behalf of Novartis

Public Comments and Discussion

Ze Cong, PhD, MPhil, MSc
Amgen
Director, Global Health Economics

Conflicts of interest:

- Receipt or potential receipt of anything of monetary value, including but not limited to, salary or other payments for services such as consulting fees or honoraria in excess of $5,000
- Status or position as an officer, board member, trustee, owner or employee of a health care company, or an organization which receives more than 25% of its funding from health care companies

Dr. Cong is a full-time employee of Amgen and holds equity interests in the company

David Mitchell
Patients for Affordable Drugs
President

Conflicts of interest:

- None declared

Patients for Affordable Drugs receives funding from the Laura and John Arnold Foundation, which is also a funder of ICER

Liz Helms
California Chronic Care Coalition
President, CEO, and Co-Founder

Conflicts of interest:

- Status or position as an officer, board member, trustee, owner or employee of a health care company, or an organization which receives more than 25% of its funding from health care companies

Liz Helms serves on the board of directors for the California Healthcare Performance and Information System (CHPI), which has received funding from Blue Shield of California among other large health plans, and the Pacific Business Group on Health (PBGH). This is a volunteer position.

Lunch

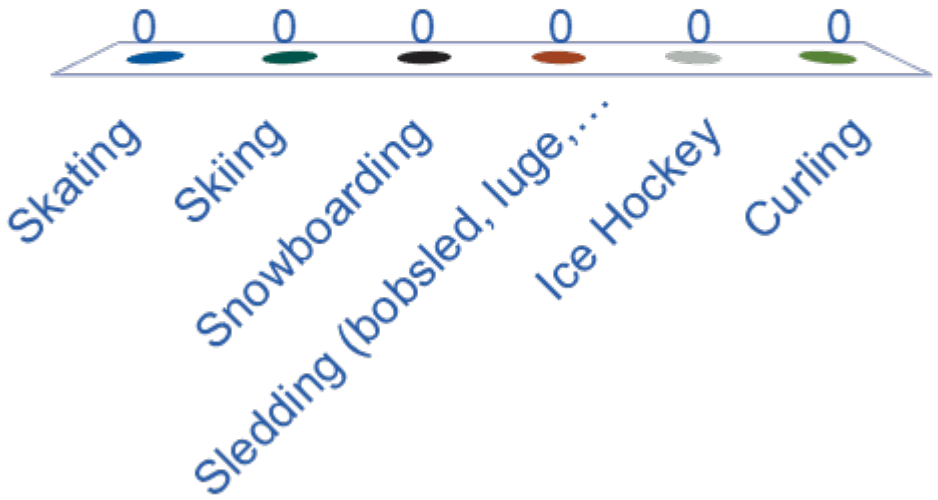
Meeting will resume at 1:00 pm

Voting Questions

WIFI: NILE
PW: 5108747582

0. What is your favorite Winter Olympic sport?

A. Skating
B. Skiing
C. Snowboarding
D. Sledding (bobsled, luge, skeleton, etc.)
E. Ice Hockey
F. Curling



Patient population for questions 1-4: Patients ages 0-25 years with B-cell acute lymphoblastic leukemia that is refractory or in second or greater relapse

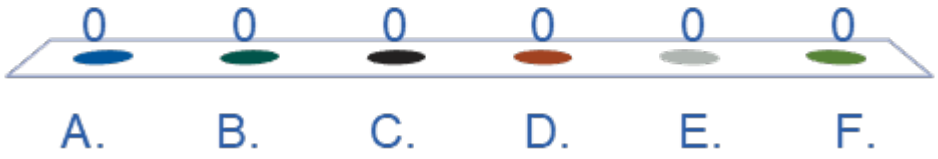
1. Is the evidence adequate to demonstrate a net health benefit for treatment with Kymriah versus treatment with clofarabine or comparable immunotherapy or chemotherapy (e.g., blinatumomab, multi-agent chemotherapy including clofarabine)?

A. Yes

B. No

2. Does treating patients with Kymriah offer one or more of the following "other benefits?" (select all that apply)

A. Reduced complexity that will significantly improve outcomes
B. Reduce important health disparities
C. Significantly reduce caregiver/family burden
D. Novel mechanism of action or approach….
E. Significant impact on improving return to work/overall productivity
F. Other…



3. Are any of the following contextual considerations important in assessing Kymriah's long-term value for money? (select all that apply)

A. Care of individuals with condition of high severity

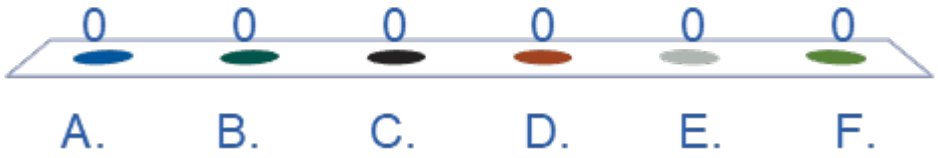
B. Care of individuals with condition with high lifetime burden of illness

C. First to offer any improvement

D. Compared to clofarabine or comparable chemo/immunotherapy, there is significant uncertainty about long-term risk of serious side effects

E. Compared to the clofarabine or comparable chemo/immunotherapy, significant uncertainty about magnitude or durability of the long term benefits of this intervention

F. Additional considerations…



4. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with Kymriah versus treatment with clofarabine?

A. Low

B. Intermediate

C. High

Patient population for questions 5-10: Patients ages 18 years and older aggressive B-cell lymphoma that is refractory or in second or greater relapse.

5. Is the evidence adequate to demonstrate a net health benefit for treatment with Yescarta versus treatment with the regimens assessed in the SCHOLAR-1 trial?

A. Yes

B. No

6. Is the evidence adequate to demonstrate a net health benefit for treatment with Kymriah versus treatment with the regimens assessed in the SCHOLAR-1 trial?

A. Yes

B. No

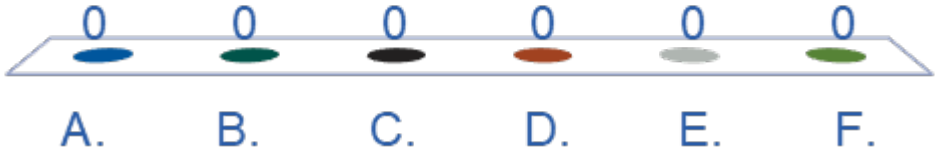
7. Is the evidence adequate to distinguish the net health benefit between Yescarta and Kymriah?

A. Yes

B. No

8. Does treating patients with Yescarta offer one or more of the following “other benefits?” (select all that apply)

A. Reduced complexity that will significantly improve outcomes
B. Reduce important health disparities
C. Significantly reduce caregiver/family burden
D. Novel mechanism of action or approach….
E. Significant impact on improving return to work/overall productivity
F. Other…



9. Are any of the following contextual considerations important in assessing Yescarta's long-term value for money? (select all that apply)

A. Care of individuals with condition of high severity

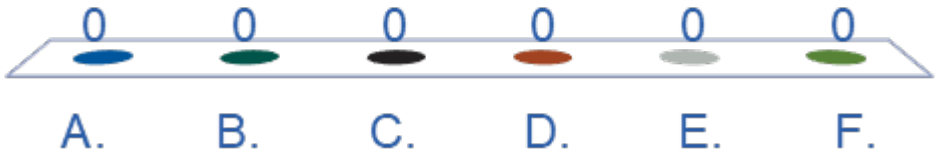
B. Care of individuals with condition with high lifetime burden of illness

C. First to offer any improvement

D. Compared to the regimens in SCHOLAR-1, there is significant uncertainty about long-term risk of serious side effects

E. Compared to the regimens in SCHOLAR-1, significant uncertainty about magnitude or durability of the long term benefits of this intervention

F. Additional considerations…



10. Given the available evidence on comparative effectiveness and incremental cost-effectiveness, and considering other benefits, disadvantages, and contextual considerations, what is the long-term value for money of treatment with Yescarta versus treatment with the regimens assessed in the SCHOLAR-1 trial?

A. Low

B. Intermediate

C. High

Policy Roundtable

Policy Roundtable Participants

Name	Title	COI Declaration
Emily Dumler	Patient Advocate	None
Denise Globe, PhD	Vice President and Head of Health Economics and Outcomes Research, US Oncology, Novartis Pharmaceuticals	**Full-time employee, equity interests**: Novartis
Michelle Hermiston, MD, PhD	Associate Professor, Department of Pediatrics (Hematology/Oncology); Department of Pediatric Hematology/Oncology; Director, Pediatric Immunotherapy Program, UCSF School of Medicine and UCSF Helen Diller Family Comprehensive Care Center	**Employment, equity interests**: Dr. Hermiston's spouse was employed/holds equity interests with Bayer, and holds several patents unrelated to CAR-T, and is the founder/CEO of Coagulant Therapeutics
Krishna Komanduri, MD	Kalish Family Chair in Stem Cell Transplantation; Professor of Medicine, Microbiology, and Immunology; Director, Adult Stem Cell Transplant Program, University of Miami Miller School of Medicine and President, American Society for Blood and Marrow Transplantation	**Advisory boards**: Kite, Juno, Sanofi, Novartis **Data Safety monitoring board**: Novartis (unrelated to CAR-T) **Educational activity**: Merck **Sub-investigator on clinical trials**: Kite, Juno, Adaptimmune, Atara Therapeutics
Jennifer Malin, MD, PhD	Senior Medical Director, Oncology and Genetics, United Healthcare	**Full-time employee, equity interests**: UHC
Rocio Manghani, MPH	Senior Director, Payer Relations and Market Access, Kite Pharma (A Gilead Company)	**Full-time employee, equity interests**: Kite Pharma
Kimberly Schuetz	Patient Advocate	None
John Yao, MD, MPH, MBA, MPA, FACP	Staff Vice President of Medical Policy, Anthem	**Full-time employee, equity interests**: Anthem

CTAF Panel Reflections and Closing Remarks

Next Steps

- Meeting recording posted to ICER website next week
- Final Report published on March 23
  - Includes description of CTAF votes, deliberation; policy roundtable discussion
- Materials available at

  https://icer-review.org/topic/car-t/

Adjourn