KYMRIAH® (tisagenlecleucel) suspension for intravenous infusion

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Financial Disclosures

- *I am a paid employee of Novartis (major interest)*
  - *Novartis Oncology, Health Economics and Outcomes Researcher*

- *Conflict of Interest Disclosures*
  - *Novartis manufactures KYMRIAH, first FDA-approved CAR T-cell therapy*

  - *I have no intellectual conflicts of interest to report that may pertain in any way to the subject of this meeting*

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Patient Reported Outcomes (PROs)

- **CMS is seeking MEDCAC Panel recommendations on how existing PRO assessment tools should be incorporated into future clinical studies, including future clinical studies on CAR T-cell therapy**
  - "*A PRO is a measurement based on a report that comes from the patient (i.e., study subject) about the status of a patient's health condition without amendment or interpretation of the patient's report by a clinician or anyone else*" [1]

- **KYMRIAH PRO data was collected during drug development process to incorporate the patient's perspective**
  - Novartis used validated and relevant PRO measures in the Kymriah registrational studies in leukemia and lymphoma to measure the change in quality of life from the patient's perspective
  - PRO data from both trials were reported to regulatory agencies and presented at healthcare professional conferences

- **Mandating patient reported outcomes (PROs) data collection for CAR-T is unnecessary, impractical, and imposes a significant burden on providers and patients outside of clinical studies**

Reference: 1) Food & Drug Administration. Clinical Outcome Assessment (COA): Glossary of Terms. Page last updated: 02/07/2018. Accessible online.

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KYMRIAH: First FDA-Approved CAR T-Cell Therapy

- **KYMRIAH is FDA approved for the following indications:**

INDICATIONS	FDA APPROVAL
Treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse (referred to as “r/r ALL”)	8/30/2017
Treatment of adult patients with relapsed or refractory (r/r) large B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (collectively referred to as “r/r DLBCL”); KYMRIAH is not indicated for treatment of patients with primary central nervous system lymphoma	5/1/2018

KYMRIAH is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) via a limited network of certified treatment centers

- **Across both indications, patients received KYMRIAH in both the hospital outpatient and inpatient settings during the clinical trials**
  - 27% of patients in the JULIET study received KYMRIAH in the hospital outpatient setting as described in the physician prescribing information
- **Site of care for patients should be determined by their treating physician**

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High Burden of Disease for Patients With R/R ALL and R/R DLBCL

R/R ALL	R/R DLBCL
ALL is diagnosed in ~3000 children in the US	**DLBCL is diagnosed in ~27,650 patients in the US**
Despite 80% cure rates after front-line therapy pALL remains the leading cause of childhood mortality due to malignancy	**~50% to 60% of patients with DLBCL achieve and maintain complete response (CR) after first-line therapy**
R/R ALL population: ~450	**R/R DLBCL population: ~6,000**
Median age: 15 years	**Median age: 64 years**

- Patients with R/R ALL and R/R DLBCL have a very poor prognosis and high burden of disease
- KYMRIAH PRO Instruments utilized in registration trials were incorporated to measure the change in disease burden from the patient's perspective

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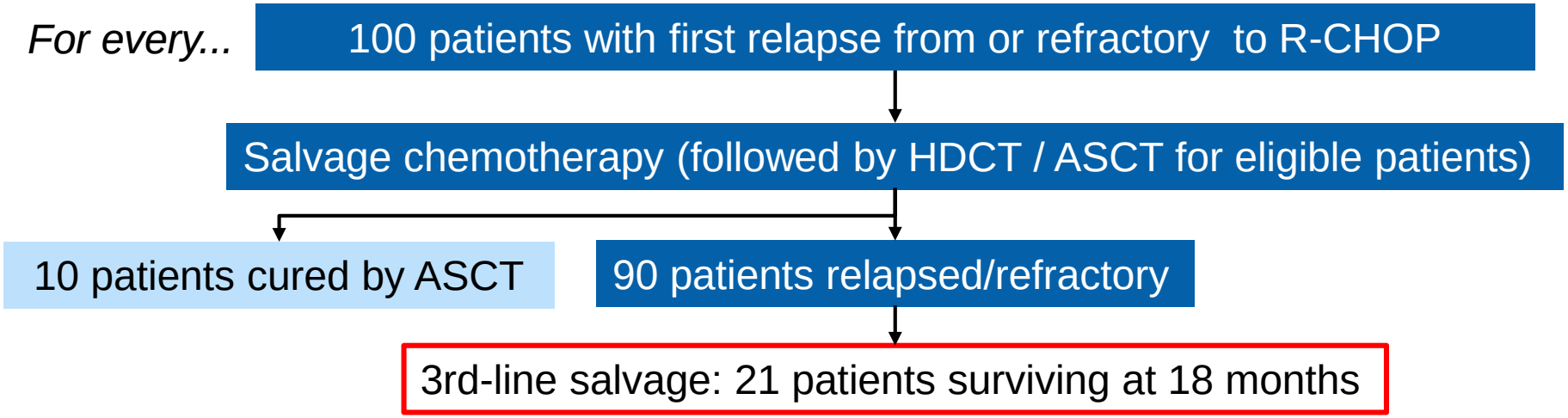
DLBCL Treatment Landscape

- **SOC for patients with r/r DLBCL is high-dose chemotherapy followed by auto-SCT[3,4]**
  - Only about a quarter of these patients can receive a transplant[3,4]
- **Patients with refractory DLBCL have a poor prognosis**
  - Low rate of response to salvage therapy (CR 8%; PR 18%)[5]
  - Short survival (median OS 4 to 6 months)[5,6]



References: 1. Rovira J et al. *Ann Hematol.* 2015;94(5):803-812. **2.** Perry AR, Goldstein AH. *Annals of Oncol.* 1998:9(Suppl. I):S9-S14. **3.** Schuster SJ et al; on behalf of the JULIET study investigators. Primary analysis of JULIET: a global, pivotal, phase 2 trial of tisagenlecleucel (CTL019) in adult patients with relapsed or refractory diffuse large B-cell lymphoma. Presented at: 59th American Society of Hematology Annual Meeting & Exposition; December 9-12, 2017; Atlanta, GA. **4.** Friedberg JW. *Hematology AM Soc Hematol Educ Program*. 2011;2011(1):498-505. **5.** Crump M, et al. *Blood.* 2017;130(16):1800-1808. **6**. Van den Neste E, et al. *BMT*. 2016;51:51-57.

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ELIANA: Overall Remission Rate

Efficacy in pediatric and young adult patients with r/r B-cell ALL[1,2]

	Efficacy Analysis Set (N = 75)
Primary end point	n (%)
ORR (CR+CRi) within 3 months[a]	61 (81)
Best overall response (BOR), n (%)	
CR[b]	45 (60)
CRi[c]	16 (21)
No response	6 (8)
Unknown	8 (11)
CR or CRi with MRD-negative bone marrow[d,e]	61 (81)

- These data are based on an updated analysis of ELIANA with a median follow-up of 13.1 months. This differs from the Prescribing Information, which included 63 infused patients who were followed for a median of 4.8 months[1,2]

B-cell ALL, B-cell acute lymphoblastic leukemia; BOR, best overall response; CR, complete remission; CRi, CR with incomplete blood count recovery; MRD, minimal residual disease; r/r, relapsed or refractory.

[a] In patients infused with KYMRIAH ≥ 3 months prior to data cutoff. [b] CR was defined as < 5% of blasts in the bone marrow, circulating blasts < 1% in peripheral blood, no evidence of extramedullary disease, neutrophils > 1.0 × 10^9/L, platelets > 100 × 10^9/L, and no platelet and/or neutrophil transfusions within 7 days of peripheral blood sample for disease assessment. [c] CRi was defined by all the criteria for CR, except that patients had ≥ 1 of the following: neutrophils ≤1.0×10^9/L, platelets ≤100×10^9/L, or platelet/neutrophil transfusions within 7 days of peripheral blood sample for disease assessment. [d] MRD negative was defined as MRD by flow cytometry less than 0.01%. [e] The null hypothesis of MRD negative remission rate ≤ 15% was rejected.

References: 1. From Maude SL, et al. N Engl J Med. 2018;378(5):439-448. Copyright © 2018 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.2. KYMRIAH (tisagenlecleucel) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2018.

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ELIANA: AESIs in Pediatric and Young Adult R/R B-Cell ALL

AESI[a], %	ELIANA (B2202)[1]
	N = 75
CRS[b]	77
ICU admission	47
Anticytokine therapy	37
Neurological events	40
Prolonged cytopenia[c]	37
Infections	43
Febrile neutropenia	35
Tumor lysis syndrome	4

AESI, adverse event of special interest; CRS, cytokine release syndrome; ICU, intensive care unit.
[a] Occurring within 8 weeks of KYMRIAH infusion and regardless of relationship to study treatment; [b] CRS was graded using the Penn scale; [c] At day 28.

References: 1. Maude SL, et al. N Engl J Med. 2018;378:439-448; 2. Maude SL, et al. Blood. 2016;128(22) [abstract 2801]; 3. Maude SL, et al. J Clin Oncol. 2016;34(suppl) [abstract 3011]; 4. KYMRIAH (tisagenlecleucel) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2018.

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ELIANA: Health-Related Quality of Life (HRQoL)

Pediatric Quality of Life Inventory (PedsQL)	EQ-5D
• Generic assessment of health-related (HR) QoL for pediatric patients • Consists of emotional, social, school, physical functioning, psychosocial health • A total score	• Standardized measure of health state • Consists of mobility, self-care, usual activities, pain/discomfort, anxiety/depression • A visual analogue scale that records patient's self-rated overall health state

PROs were collected for patients aged ≥ 8 years

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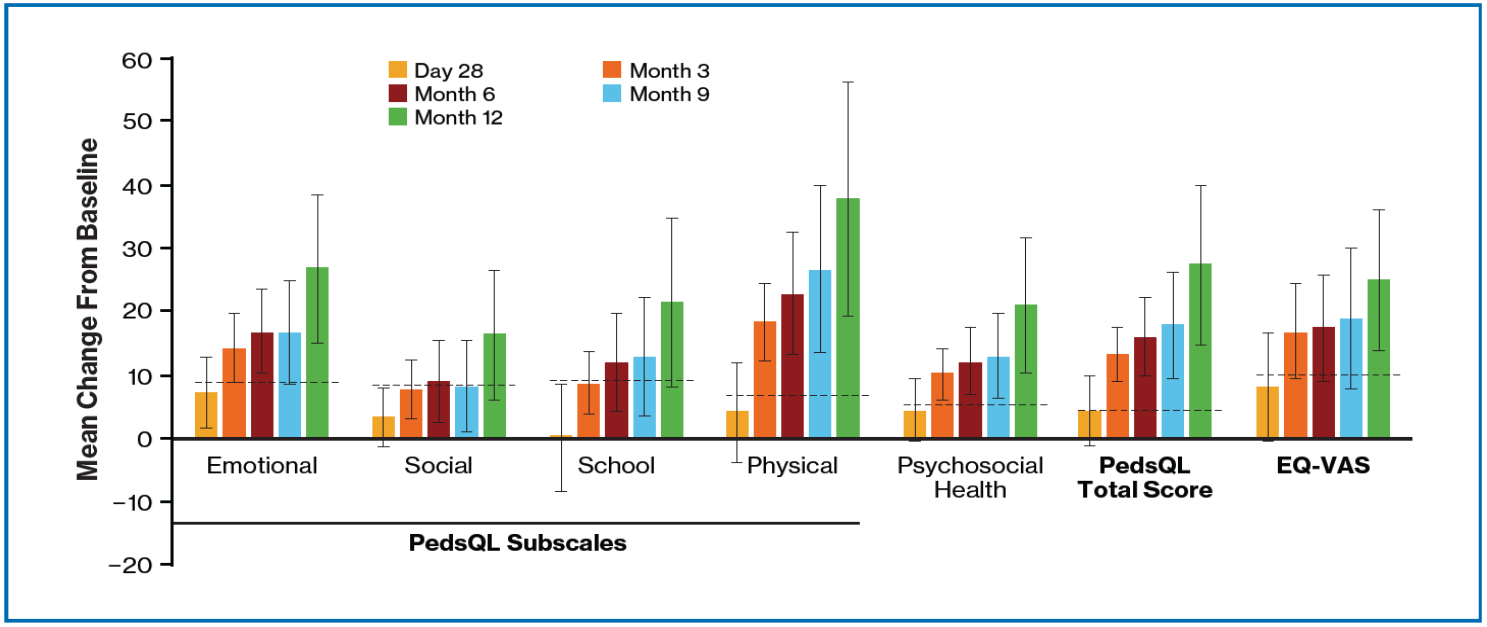
ELIANA: Health-Related Quality of Life (HRQoL)

- At months 3 and 6 after KYMRIAH infusion, the mean change in patient-reported QoL of pediatric and young adult patients with r/r B-cell ALL increased for all measures, as measured by the PedsQL and EQ VAS questionnaires (maximum score, 100)[1]



Horizontal dashed lines represent the MCIDs. Error bars represent 95% CIs, which were derived from the observed standard errors assuming a normal distribution. Analysis was based on patients with non-missing data at both baseline and the post-baseline study assessment of interest.

EQ VAS, EuroQol-visual analogue scale; QoL, quality of life.

Reference: Dietz AC, et al. In: Proceedings from the American Society of Clinical Oncology; June 2-6, 2017; Chicago, IL [abstract 10523]. Reprinted with author's permission.

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JULIET: Overall Remission Rate

- Study 1 (JULIET) Primary Endpoint: Best Overall Response Rate (ORR)
  - ORR: complete response (CR) + partial response (PR)
  - These data are from an updated analysis of the JULIET study that includes 93 patients with at least 3 months of follow-up; the median follow-up for this analysis is 14 months
  - This analysis differs from the data in the Prescribing Information, which includes a retrospectively identified subgroup of 68 patients who had not received bridging chemotherapy or who had evidence of disease after bridging chemotherapy; the median follow-up for the data included in the Prescribing Information is 9.4 months

Response Rate, %	Best Overall Response Rate (N = 93)
Best Overall Response Rate	52[a]
Complete Response Rate	**40**
Partial Response Rate	11

[a] *P* < .0001; (95% CI, 42%-64%). Null hypothesis of ORR ≤ 20%.

- Substantially improved complete response rates were observed after KYMRIAH infusion, as compared to SCHOLAR-1

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JULIET: AESIs in Adult Patients with R/R DLBCL

	KYMRIAH USPI Analysis[1] Patients (N = 106)	
AESI[a]	**All Grades, %**	**Grade ≥ 3, %**
CRS[b]	74	23
Neurological events	58	18
Prolonged cytopenia[c]		
Thrombocytopenia	—	40
Neutropenia	—	25
Infections[d]	42	25
Febrile neutropenia	17	17
Tumor lysis syndrome	1	1[e]

- The overall safety profile for the updated analysis is consistent with the previously reported AE data; variances in reported prevalence of AEs are due to different definitions of AE terms and approaches to classifying symptoms
  - In an updated analysis (N = 111), the most common AESIs[f] were CRS[b] (58%; 14% grade 3 and 8% grade 4), neurological events (21%, 7% grade 3 and 5% grade 4), prolonged cytopenias[c] (44%; 16% grade 3 and 16% grade 4), infections (34%; 18% grade 3 and 2% grade 4), and febrile neutropenia (15%; 13% grade 3 and 2% grade 4)[2]

[a] Suspected to be KYMRIAH related occurring anytime after tisagenlecleucel infusion. [b] CRS was graded using the Penn scale. [c] Not resolved by day 28. [d] Pathogen unspecified. [e] Novartis data on file. [f] Occurring within 8 weeks of tisagenlecleucel infusion.
AESI, adverse events of special interest; CRS, cytokine release syndrome.
1. KYMRIAH (tisagenlecleucel) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; 2018. 2. Borchmann P, et al. *Haematologica.* 2018;103(s2) [abstract S799] [oral presentation].

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JULIET: Health-Related Quality of Life (HRQoL)

Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym)

- FACT-Lym is a lymphoma-specific measure developed and validated for use in lymphoma patients:
  - Population: Adult (18+)
  - Recall period: past 7 days
  - Responses: 5-point Likert Scale: 0 (Not at all) to 4 (Very much)
  - Available in 48 languages
  - JULIET administration schedule: screening, months 3, 6, 12, 18, and 24

FACT-Lym: Disease-Specific Item Content

- 4 subscales from FACT-G:
  - PWB: Physical Well-being (7 items)
  - SWB: Social / Family Well-being (7 items)
  - EWB: Emotional Well-being (6 items)
  - FWB: Functional Well-being (7 items)
- 1 subscale from FACT-LymS: lymphoma-specific concerns (15 items)

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JULIET: Health-Related Quality of Life (HRQoL) (cont)

- **Clinically meaningful improvements in QoL of adult patients with r/r DLBCL were observed using the disease-specific FACT-Lym at month 3 and 6 after KYMRIAH in patients achieving PR or CR**
  - Improvements in HRQoL observed at month 3 after one-time KYMRIAH infusion, despite initial toxicity
  - Clinically important improvement from baseline observed through 6 months of follow-up

		BL Score, mean (SD)		Change From BL Score at Month 3, mean (SD)	Change From BL Score at Month 6, mean (SD)
	MCID	All Patients N = 76	Patients With CR or PR n = 40	Patients With CR or PR n = 27	Patients With CR or PR n = 16
FACT-G TS[a]	3-7	77.4 (16.0)	78.5 (15.7)	7.1 (11.9)	3.8 (14.8)
FACT-LymS	2.9-5.4	44.2 (9.0)	44.9 (9.2)	3.9 (7.5)	3.0 (6.0)
FACT-Lym TOI	5.5-11	81.4 (19.0)	83.1 (19.1)	8.1 (14.6)	5.9 (14.2)
FACT-Lym TS[a]	6.5-11.2	121.1 (23.8)	123.4 (23.9)	11.8 (17.2)	6.8 (19.8)

BL, baseline; CR, complete response; FACT-G, Functional Assessment of Cancer Therapy-General; FACT-Lym, FACT-Lymphoma; FACT-LymS, lymphoma subscale; MCID, minimal clinically important difference; PR, partial response; TOI, trial outcome index; TS, total score.

[a] 26 patients completed the FACT-Lym TS and FACT-G TS portions.

Reference: Maziarz RT, et al. In: Proceedings from the European Society for Blood and Marrow Transplantation; March 18-21, 2018; Lisbon, Portugal [abstract A034]. Reprinted with author's permission.

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JULIET: Health-Related Quality of Life (HRQoL)

36-Item Short Form Health Survey (SF-36)

- Measure HRQoL among healthy individuals and patients with acute and chronic conditions
- Consists of:
  - physical functioning
  - role-physical
  - bodily pain
  - general health
  - Vitality
  - social functioning
  - role-emotional
  - mental health
- Two summary scores: physical and mental component
- Widely-used general HRQoL measure allows comparison to gender and age-based norms, as well as across diseases; supported by international HTA organizations

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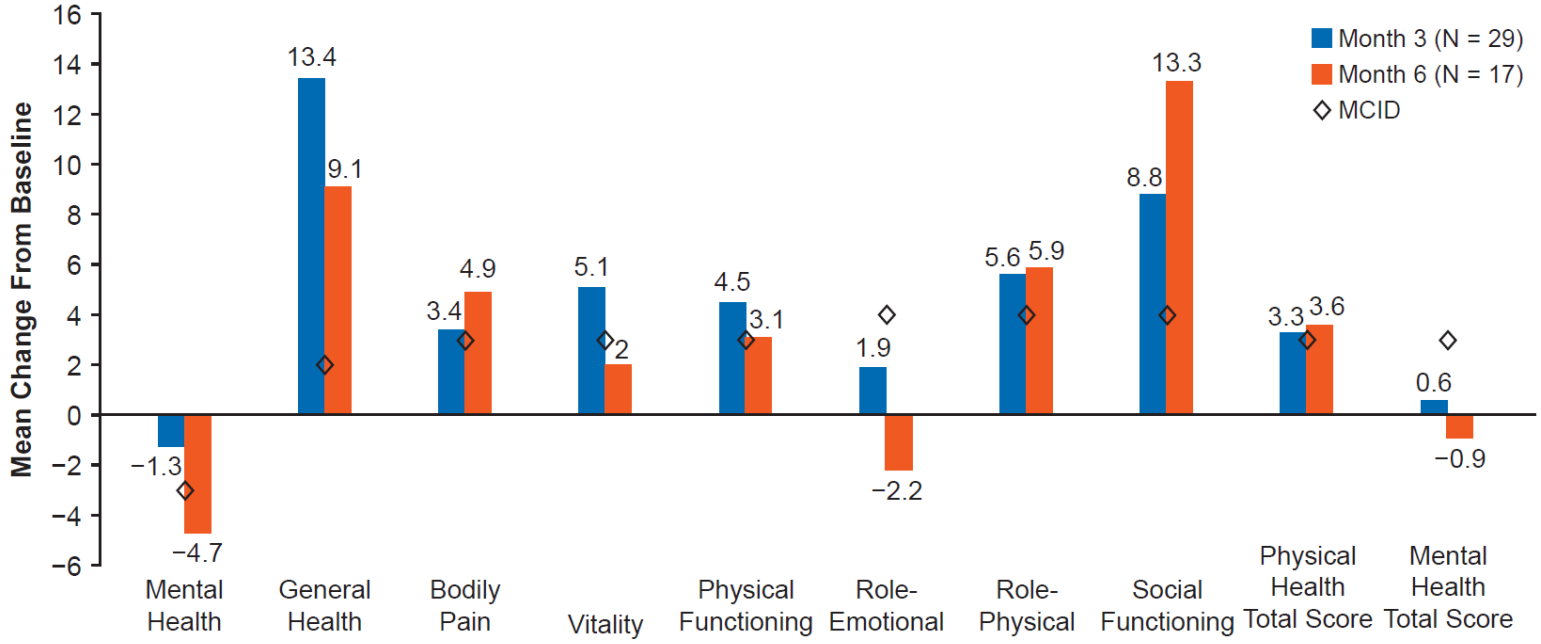
JULIET: Health-Related Quality of Life (HRQoL)

- **Clinically meaningful improvements in QOL of adult patients with r/r DLBCL were observed using Short Form-36 at month 3 and 6 after KYMRIAH in patients achieving PR or CR**
  - Mental health was the only subscale that did not improve over baseline at either month 3 or month 6



MCID, minimal clinically important difference; QoL, quality of life.

From Maziarz RT, et al. In: Proceedings from the European Society for Blood and Marrow Transplantation; March 18-21, 2018; Lisbon, Portugal [abstract A034]. Reprinted with author's permission.

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Logistical and Administrative Considerations* When Administering PRO in Clinical Research

Preparing

- Protocol design
- Research objective
- Patient population
- Language needs assessment
- Instrument licensing contracts and fees
- Data collection forms
- Validation of electronic data collection (ePRO)
- IRB approval
- Statistical analysis and reporting plan

Collecting

- Site personnel training
- Adequate supply of data collection form
- Linguistically validated translations
- Patient authorization and consent
- Quality and completeness checks
- Plans for redundancy (e.g. paper back-up for e-PRO)

Reporting

- Data entry
- Data systems requirements and back-up
- Data privacy and security
- Data reporting transfer
- Data validation
- Appling rules for missing data
- Data reporting and interpretation

*Not an exhaustive list

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Mandating PRO data collection for CAR-T is unnecessary

Context-Specific	**Single PRO is inappropriate for all potential CAR-T treatment areas**	• *CAR-T has applications beyond oncology* • *AEs, Symptoms and burden will vary by disease area* • *Therefore, PRO instruments vary by disease and patient population (i.e. pediatric vs. adult vs. elderly adult)*
Sufficient evidence	**Positive benefit risk ratio established by FDA**	• *Efficacy, safety, and PRO data from Kymriah trials established positive benefit risk ratio* • *PRO data was and is being collected, and data will continue to mature* • *Long-term safety and efficacy will be reported under registry for Kymriah* • *PRO data from long-term follow-up studies will be reported overtime*
Administrative & Financial Burden	**PRO collection imposes significant burden on providers and patients**	• *Significant administrative burden on centers to collect and report PRO data outside clinical trials. In addition, not all centers are equipped for this complex activity* • *Substantial financial burden borne by centers to build infrastructure for PRO collection* • *Additional burden for patients and family in diseases with extremely poor conditions*
Data Quality Challenge	**Incomplete data likely due to patient condition & care setting**	• *R/R patients in poor conditions likely result in substantial missing PRO data* • *Patients receive care at different facilities during their disease journey; this will likely contribute to incompleteness of PRO data*
Beneficiary Access Delay/Deny	**Mandating PRO collection may impede beneficiary access**	• *Mandating PRO collection may delay access due to required build of infrastructure for PRO collection at centers, lack of center participation due to administrative and financial burden, and incomplete PRO data may make access decisions difficult*

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Summary

- **Patients with R/R ALL and R/R DLBCL have a very poor prognosis and high burden of disease**
- **KYMRIAH PRO Instruments utilized in registration trials were incorporated to measure the change in disease burden from the patient's perspective**
  - In patients who respond to KYRMIAH, clinically meaningful improvements in HRQoL were observed in both ELIANA and JULIET trials, consistent with primary clinical endpoints within the trial
- **Mandating PRO data collection for CAR-T is unnecessary, impractical, and imposes a significant burden on providers and patients**

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