# CAR-T Cell Therapy Registry

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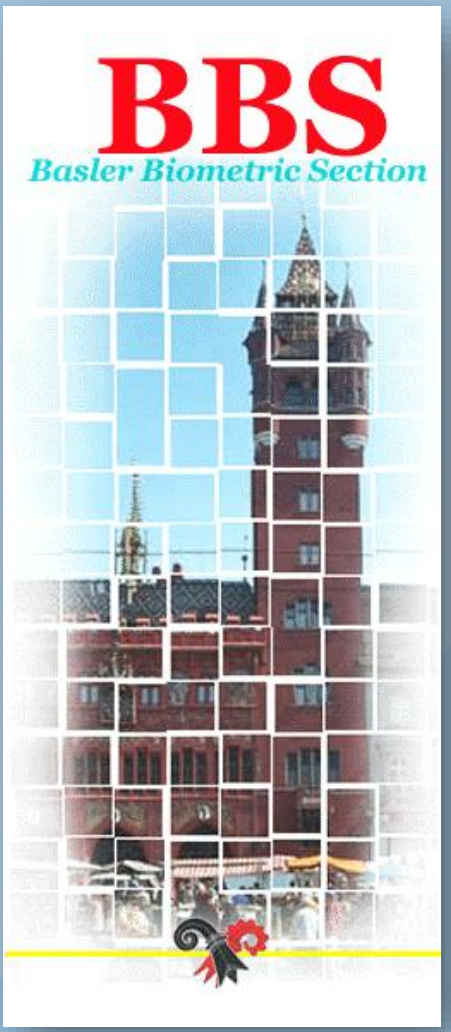


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# Conflict of Interests to Disclose

- *Marcelo C Pasquini, MD, MS*

*Professor of Medicine, Medical College of Wisconsin*

*Principal Investigator, Cellular Immunotherapy Data Resource (CIDR)*

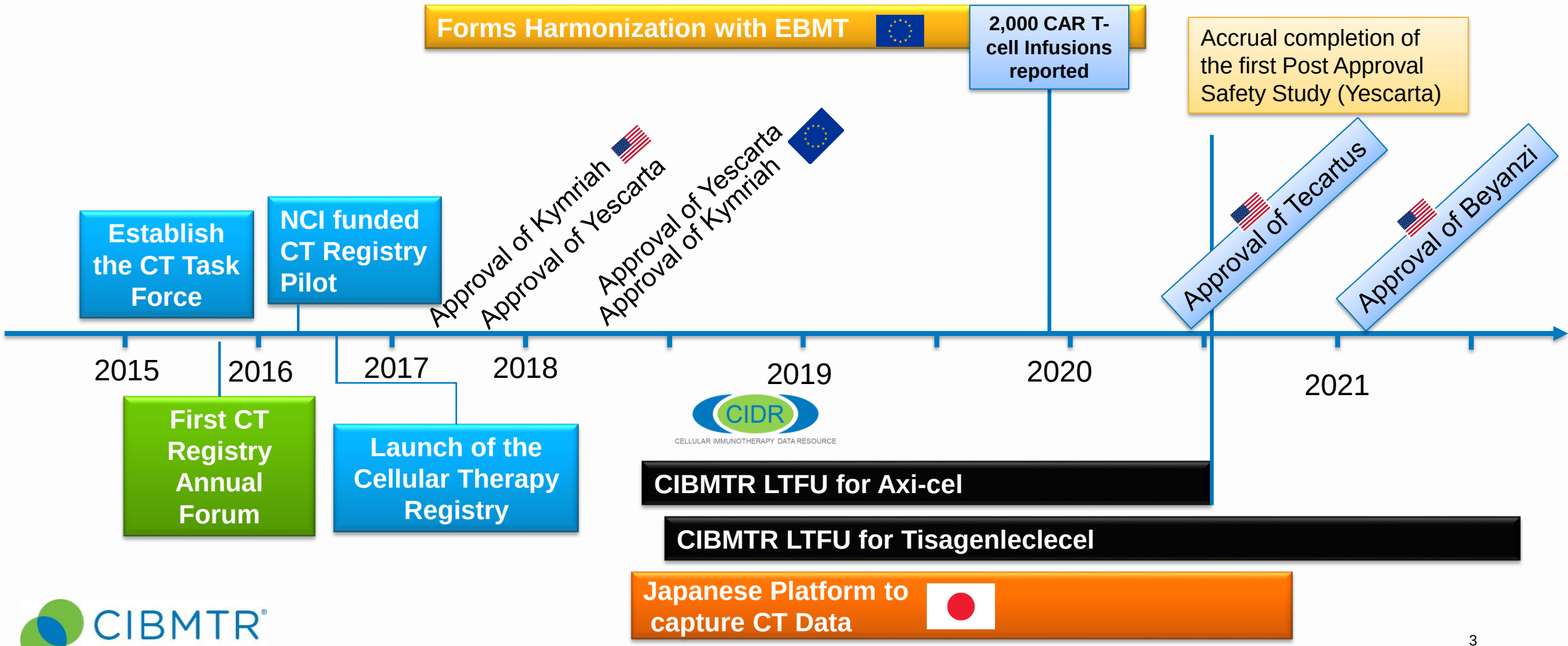
- **Research Support**: Bristol Myers Squibb (BMS), Kite Pharma and Novartis
- **Consultant:** BMS

- *Zhen-Huan Hu,  MPH*

*Senior Statistician, Cellular Therapy Lead – CIBMTR/CIDR*

- ***No relevant conflict of interests to disclose***

# Timeline and Milestones of CT Registry



# Number of CAR T cell infusions: 2016-2021 (3,773 patients and 3,976 infusions)

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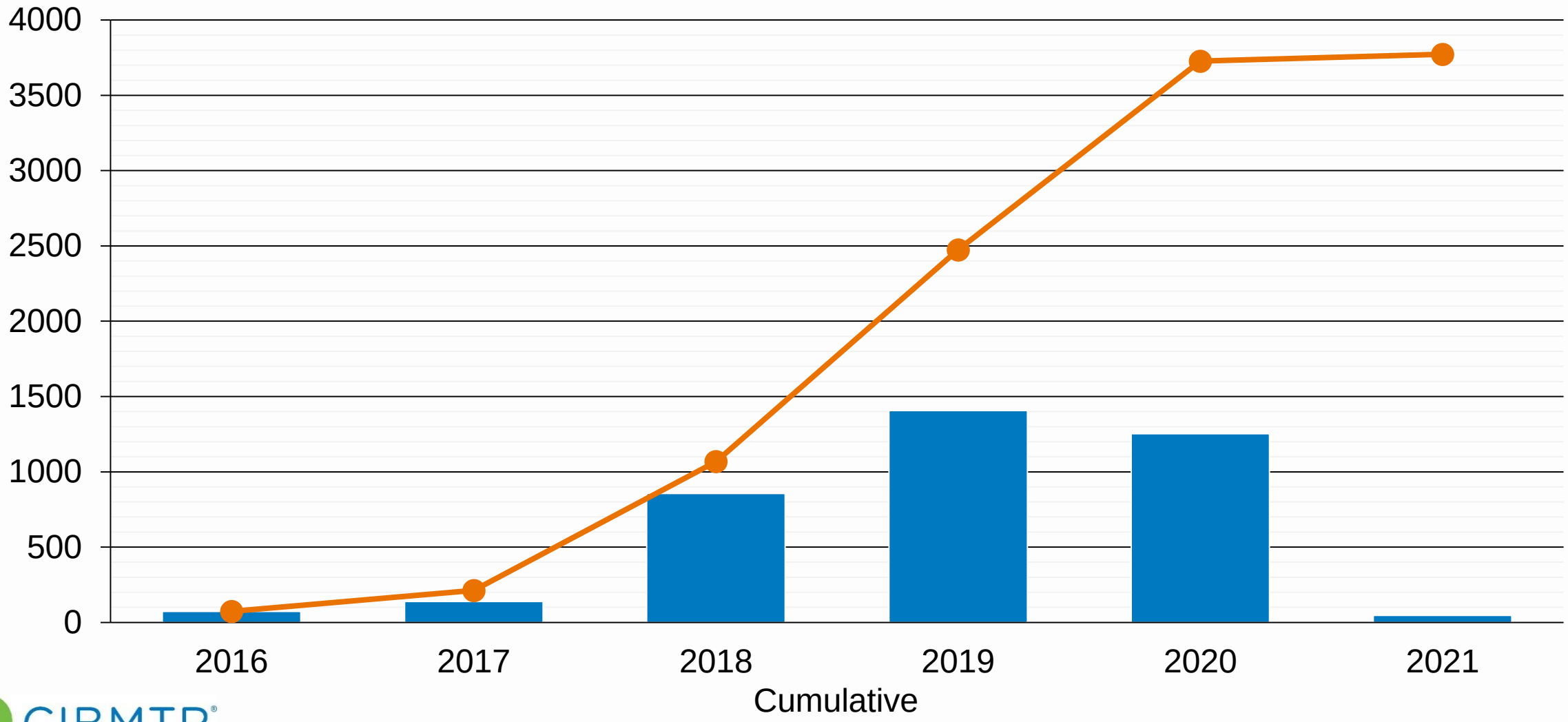


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Data Incomplete for 2020 & 2021

# CAR T Cell Indications: 2016-2021 (N=3,773)

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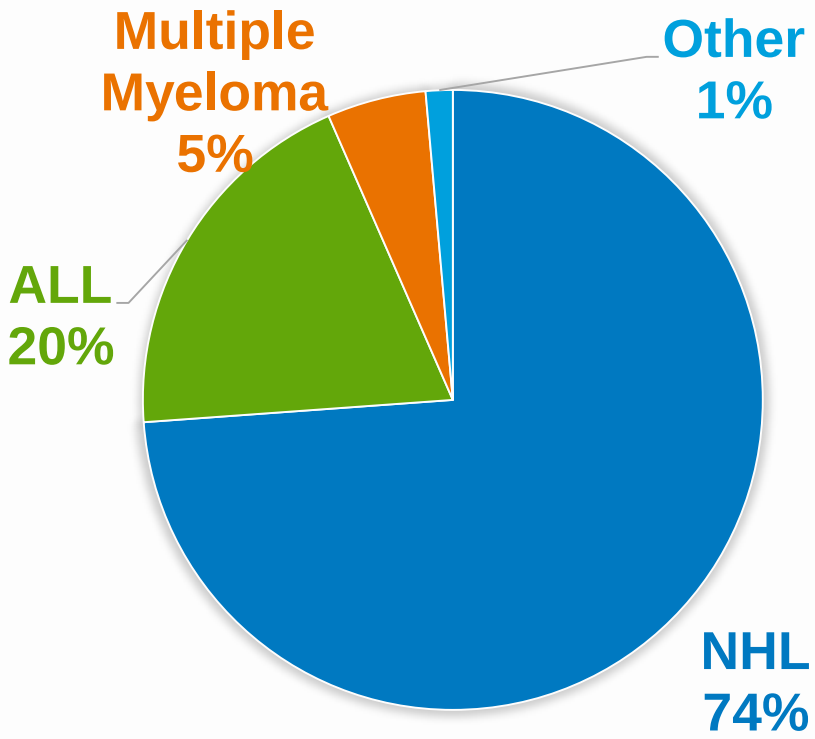


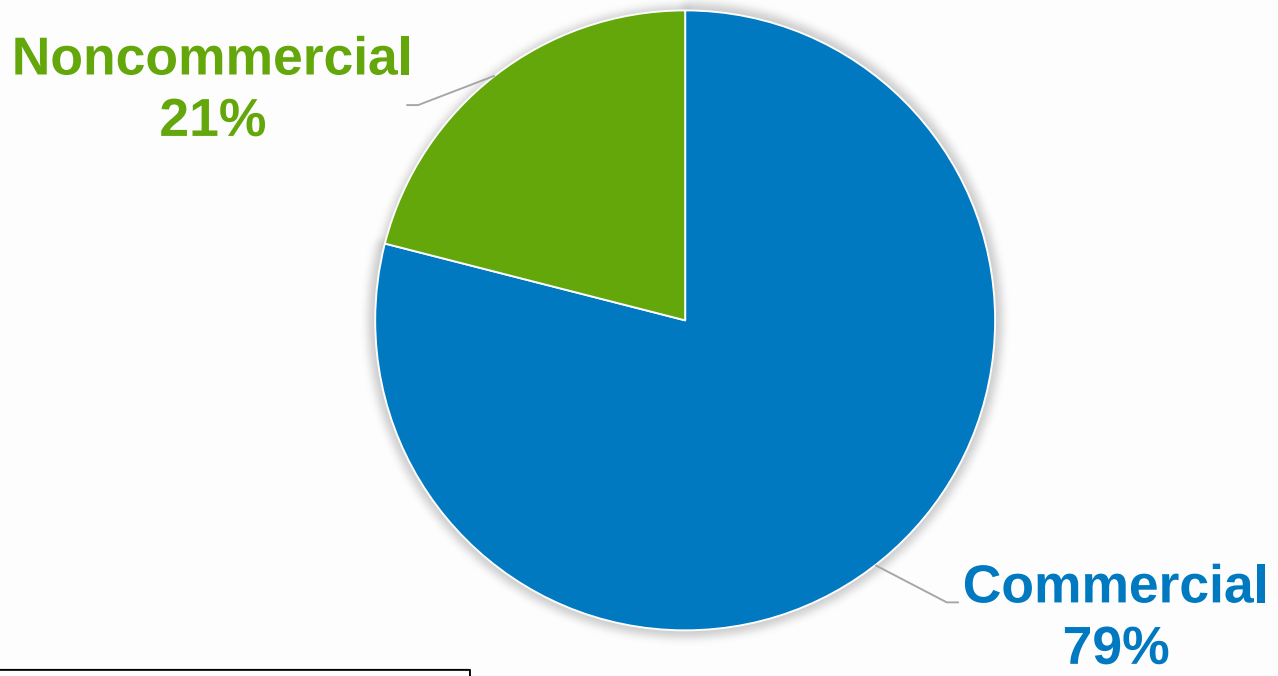


Centers: 157
Median age: 59 y (<1-91)y
Prior HCT: 33%

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# Industry-sponsored Projects

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| Project | Sponsor | Objective | Timeline/Duration |
|---|---|---|---|
| **Yescarta LTFU (Axicabtagene ciloleucel)** | **Kite** | Safety and efficacy outcomes (PASS)<br>**N=1,500 (*Completed 07/2020*)**<br>**Diseases: LBL** | **07/2018**<br>***2*** years of accrual<br>**15** years of follow up |
| **Kymriah LTFU (Tisagenlecleucel)** | **Novartis** | Safety and efficacy outcomes (PASS)<br>**N=2,500** (*Current N=1000*)<br>**Diseases: NHL and ALL** | **08/2018**<br>**5** years of accrual<br>**15** years of follow up |
| **Lisocabtagene maraleucel** | **BMS** | Safety and efficacy outcomes (PASS)<br>**N=1,000 Disease: NHL** | **5** years<br>**15** years of follow up |
| ***Under Development*** | | | |
| **Idecabtagene vecleucel** | **BMS** | Safety and efficacy outcomes (PASS)<br>**N=1,000 Diseases: Multiple Myeloma** | **5** years<br>**15** years of follow up |
| **Tecartus (Brexucatagene autoleucel)** | **Kite** | Safety and efficacy outcomes (PASS)<br>**N=500 Disease: Mantle Cell Lymphoma** | **5** years<br>**15** years of follow up |
| **Ciltacabtagene autoleucel** | **Janssen/ Legend** | Safety and efficacy outcomes (PASS)<br>**N=TBD Disease: Multiple Myeloma** | **5** years<br>**15** years of follow up |

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# Statistical Challenges in the Clinical Development of CAR-T Cell Therapies - Registry

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# Baseline Information Available in Registry

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- Patient-related
  - Age, sex, race/ethnicity
  - Comorbidities
  - KPS prior to infusion
- Disease-related
  - Sub-disease at diagnosis
  - Disease status prior to infusion
  - Cytogenetics
  - Lab values (CBC, blast %, etc)
- Therapy-related
  - Prior lines of therapies
  - LD chemo
  - Time of leukapheresis

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# Outcomes Derived from Registry Data

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- Safety outcomes
  - CRS
  - ICANS
  - Prolonged cytopenia
  - Grade 3-4 organ toxicities
  - Hypogammaglobulinemia
  - Tumor lysis syndrome
  - Serious infections
  - Subsequent neoplasm
  - Pregnancy
- Efficacy outcomes
  - Best overall response (BOR)
  - Duration of response (DOR)
  - Relapse/disease progression
  - Disease-free survival/progression-free survival (DFS/PFS)
  - Overall survival (OS)

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# Duration of Follow-Up

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- Currently, one of the main challenges for registry studies.
- As of Feb 28, 2021:
  - 2,472 out of 2,997 (82%) patients receiving commercial CAR-T products reported at least one follow-up
  - Median follow-up of survivors: 11.9 (0.8-37.0) months
- Improving over time.

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# Data Imbalance

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- Unlike clinical trials, the baseline characteristics of patients from the registry may not be completely balanced between two treatment groups.
  - e.g.: Patient population receiving one CAR-T products may be older than those receiving the other products.
- Solutions:
  - Matching/stratification
  - Multivariate regression models (logistic regression, Cox proportional hazard model, direct adjusted survival estimates)
  - Propensity score (propensity score matching, inverse probability of treatment weighting)

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# Censoring and Competing Risks

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- Censoring events
  - Alive at the last follow-up
  - Subsequent HCTs
  - Subsequent CTs
  - Other subsequent anti-cancer therapies
- Competing risk events
  - Death without experiencing the event of interest
  - Subsequent HCTs
  - Subsequent CTs
  - Other subsequent anti-cancer therapies

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# Left-truncation in Retrospective Data

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- Left-truncation occurs when certain subjects from the underlying population are unknown to the observers when their event time fails to surpass certain time threshold.
  - e.g.: If we want to compare registry vs. clinical trial patients from the time of leukapheresis, patients who died between leukapheresis and infusion are not observable through the registry and therefore left-truncated.
- Adjust left-truncation:
  - Supported directly in SAS: Kaplan-Meier/cumulative incidence estimates, Cox proportional hazards model
  - In-house SAS macros: direct adjusted survival estimates, weighted/unweighted logrank test

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# Tisagenlecleucel Real World Data

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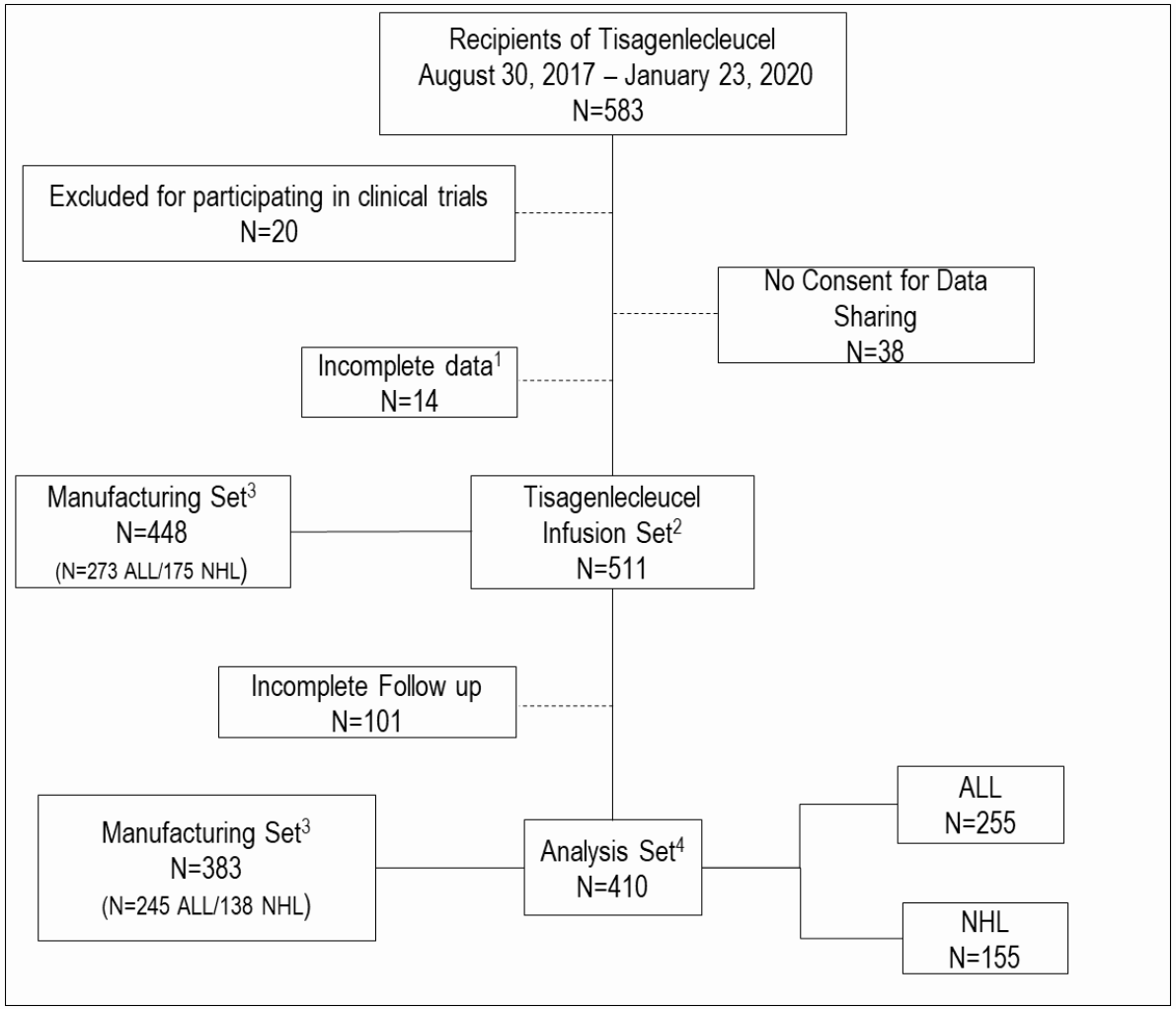


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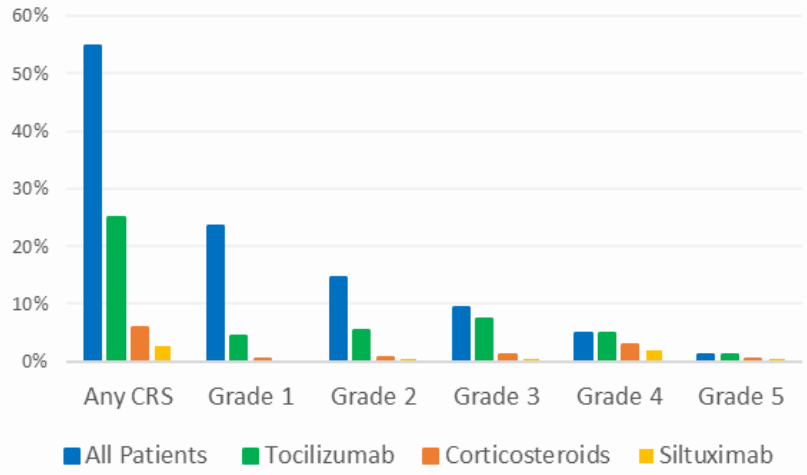
Pasquini MC et al, Blood Advances *in press*

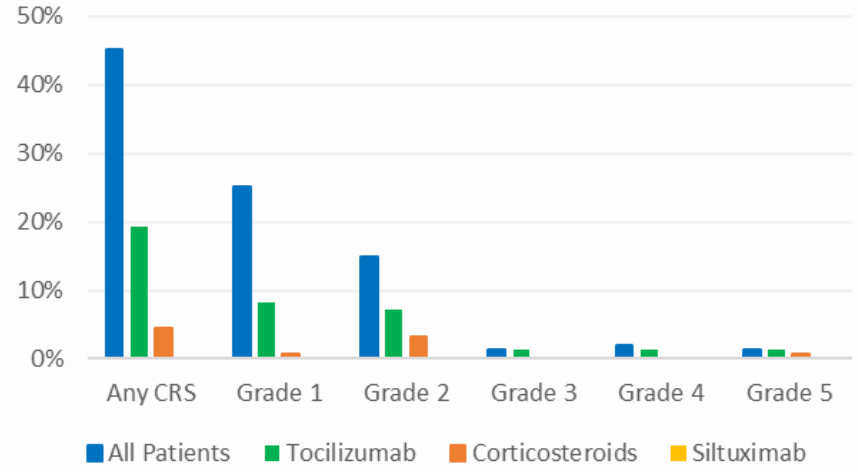
# CRS with Tisagenlecleucel by indication

| Endpoint | ALL | | NHL | |
|---|---|---|---|---|
| | CIBMTR (N=255) | ELIANA (N=79) | CIBMTR (N=155) | JULIET (N=115) |
| CRS | | | | |
| Any, n (%) | 140 (54.9) | 61 (77.2) | 70 (45.2) | 66 (57.4) |
| Grade ≥3, n (%) | 41 (16.1) | 38 (48.1) | 7 (4.5) | 26 (22.6) |
| Median time to onset in days (range) | 6 (1-27) | 7 (2-20) | 4 (1-14) | 3 (1-17) |
| Median duration in days (range) | 7 (1-76) | 4 (1-64) | 5 (1-33) | 12 (1-85) |

**B: Acute Lymphoblastic Leukemia**




**C: Non-Hodgkin Lymphoma**

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# Responses and Survival Outcomes with Tisagenlecleucel

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**B**

| Endpoint | CIBMTR (N=249), % (95% CI) | ELIANA (N=79), % (95 % CI) |
|---|---|---|
| BOR of CR | 85.5% (80.6, 89.7) | 82.3% (72.1,90.0) |
| MRD negative | 99.1% (115/116) (95.3, 100) | 100.0% (64/64) (94.4, 100) |
| DOR | | |
| At 6 mo | 78.1% (70.5, 84.0) | 80.8% (68.0, 88.9) |
| At 12 mo | 60.9% (49.4, 70.5) | 67.4% (53.2, 78.1) |
| EFS | | |
| At 6 mo | 68.6% (62.0, 74.4) | 71.7% (59.8, 80.6) |
| At 12 mo | 52.4% (43.4, 60.7) | 57.2% (44.5, 68.0) |
| OS | | |
| At 6 mo | 88.5% (83.6, 92.0) | 88.6% (79.3, 93.9) |
| At 12 mo | 77.2% (69.8, 83.1) | 77.1% (66.1, 84.9) |

**D**

| Endpoint | CIBMTR (N=152), % (95% CI) | JULIET (N=115), % (95% CI) |
|---|---|---|
| ORR (CR+PR) | 61.8% (53.6,69.6) | 52.2% (42.7, 61.6) |
| BOR of CR | 39.5% (31.6, 47.7) | 38.3% (29.4, 47.8) |
| DOR | | |
| At 6 mo | 55.3% (42.2, 66.6) | 66.6% (52.8, 77.3) |
| At 12 mo | 48.4%* (33.9, 61.5) | 62.7% (48.7, 73.9) |
| PFS | | |
| At 6 mo | 38.7% (30.5, 46.9) | 39.0% (29.7, 48.2) |
| At 12 mo | 26.4%* (17.2, 36.6) | 34.7% (25.7, 43.9) |
| OS | | |
| At 6 mo | 70.7% (62.2, 77.6) | 61.2% (51.6, 69.5) |
| At 12 mo | 56.3% (44.2, 66.8) | 48.2% (38.6, 57.1) |

*Indicates less than 10 patients at risk at this time point

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# Neurologic Symptoms and Relationship between ICANS and CRS

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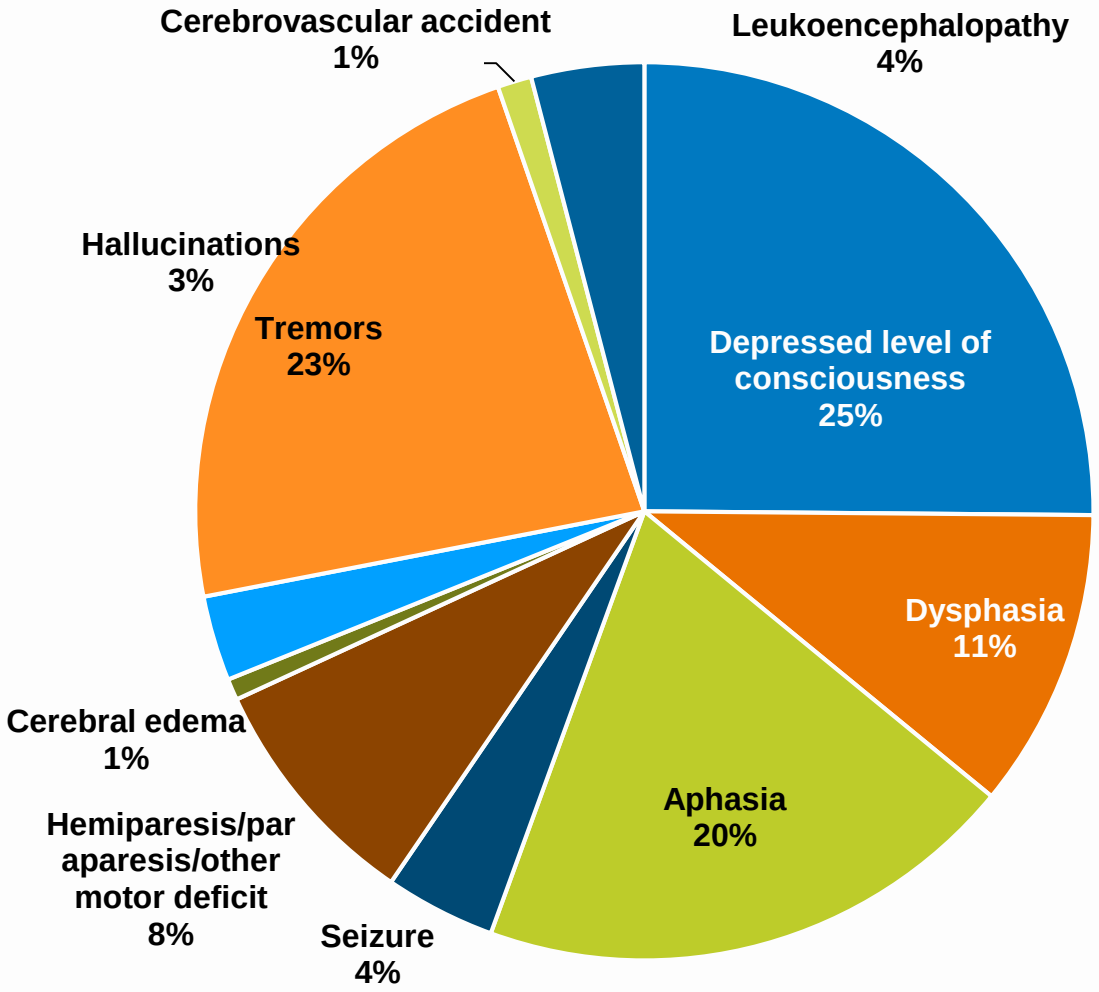


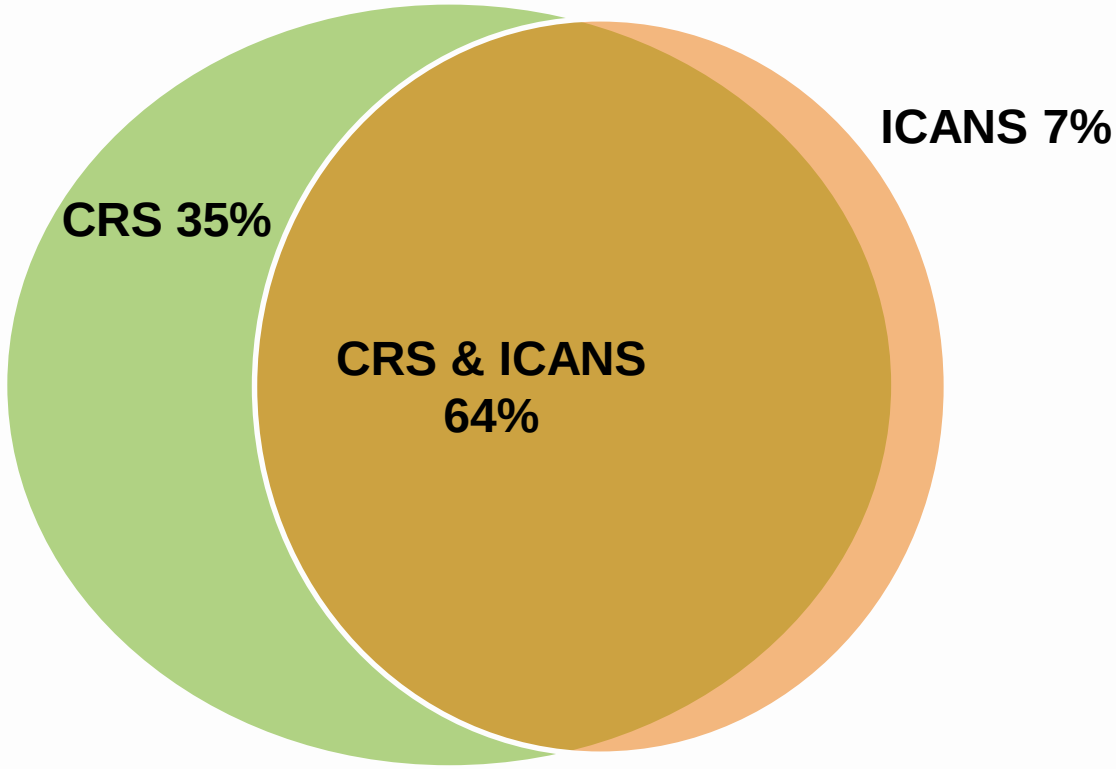


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# Conclusion

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- Cellular Therapy Outcomes Databases are now being used to meet regulatory requirements.
- CT data offers unique statistical challenges:
  - Short follow-up (improving over time)
  - Imbalanced baseline data
  - Right-censored and left-truncated time-to-event data
- Outcomes in the real-world setting are comparable to what was observed in the pivotal trials

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