Comparative effectiveness of Breyanzi/lisocabtagene maraleucel versus real-world standard of care in patients with relapsed or refractory large B-cell lymphoma

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Overview

- Context: Background, Study Objectives & Design
- Building Multi-Use Data Assets: Data Strategy and Modelling
- Data Integration and Harmonization Across Multiple Data Sources
  - Common Study Data Model
  - De-duplication
  - Operational definition challenges
- Methodologic Challenges with Index Date Assignment
- Study Results & Conclusions

Liso-cel DLBCL 3L+ Comparator Cohort: NDS_NHL_001

- DLBCL is an aggressive lymphoma accounting for ~31% of all non-Hodgkin lymphoma and 37% of B-cell lymphomas worldwide.
- Approximately 1/3 do not respect to front line therapy or achieve durable remission.
- SCHOLAR-1, large international multicohort retrospective study reported R/R DLBCL patients had ORR of 26% and CR of 7% with median OS of 6.3 months.
- Treatment landscape has improved with approval of two CAR T cell products: Yescarta & Kymriah.
- TRANSCEND NHL 001 is single arm study without active comparator; a RW comparator cohort was needed to contextualize conventional therapies for patients with R/R DLBCL.

Necessary Criteria for RWE Comparator Cohorts

- Medical urgency / inadequate standard of care
- Expected large effect size
- Small patient population
- Rapid entry of new therapies / Standard-of-Care changes often
- Endpoints measurable with Real-World Data

Objectives

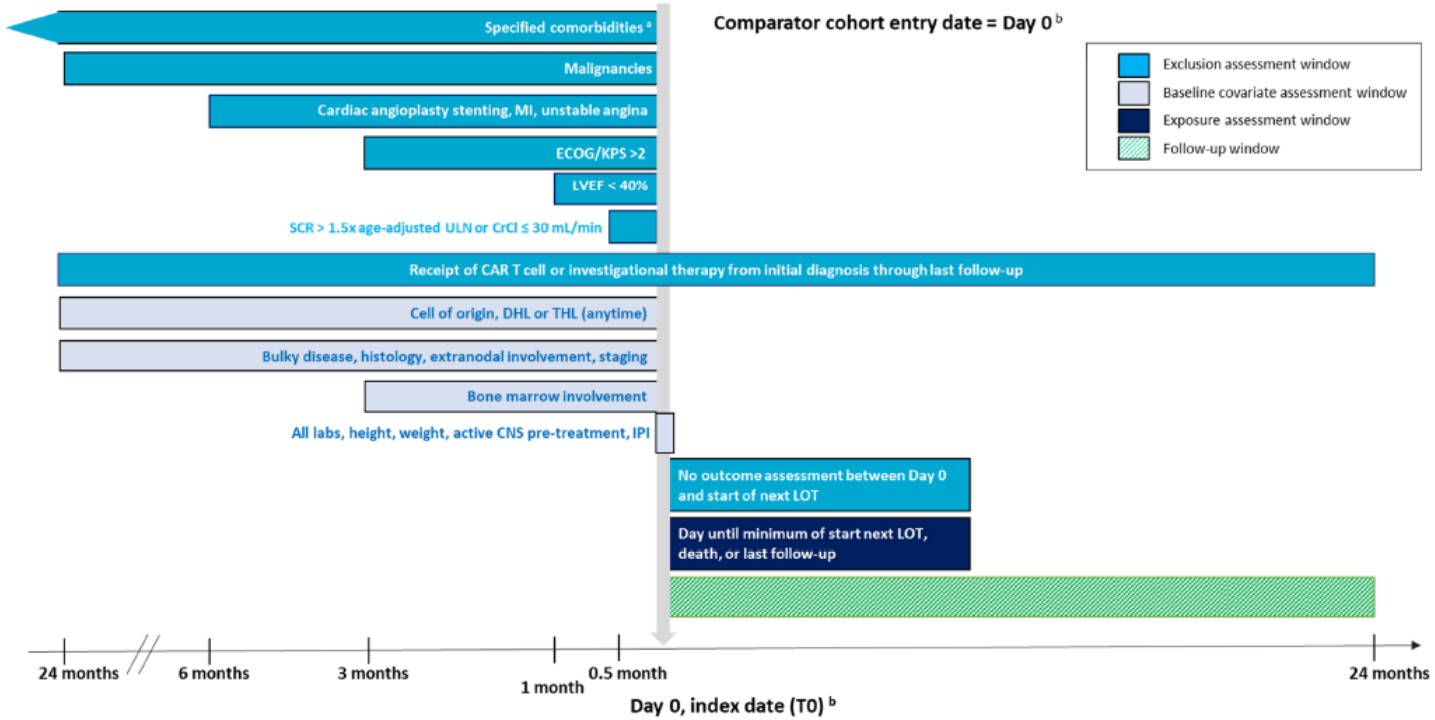
Primary objective: To describe demographic and clinical characteristics, treatment patterns and clinical outcomes of subjects with R/R B-NHL who are treated in RW clinical oncology settings.

Secondary objective: To assess the comparative effectiveness of liso-cel versus external controls.

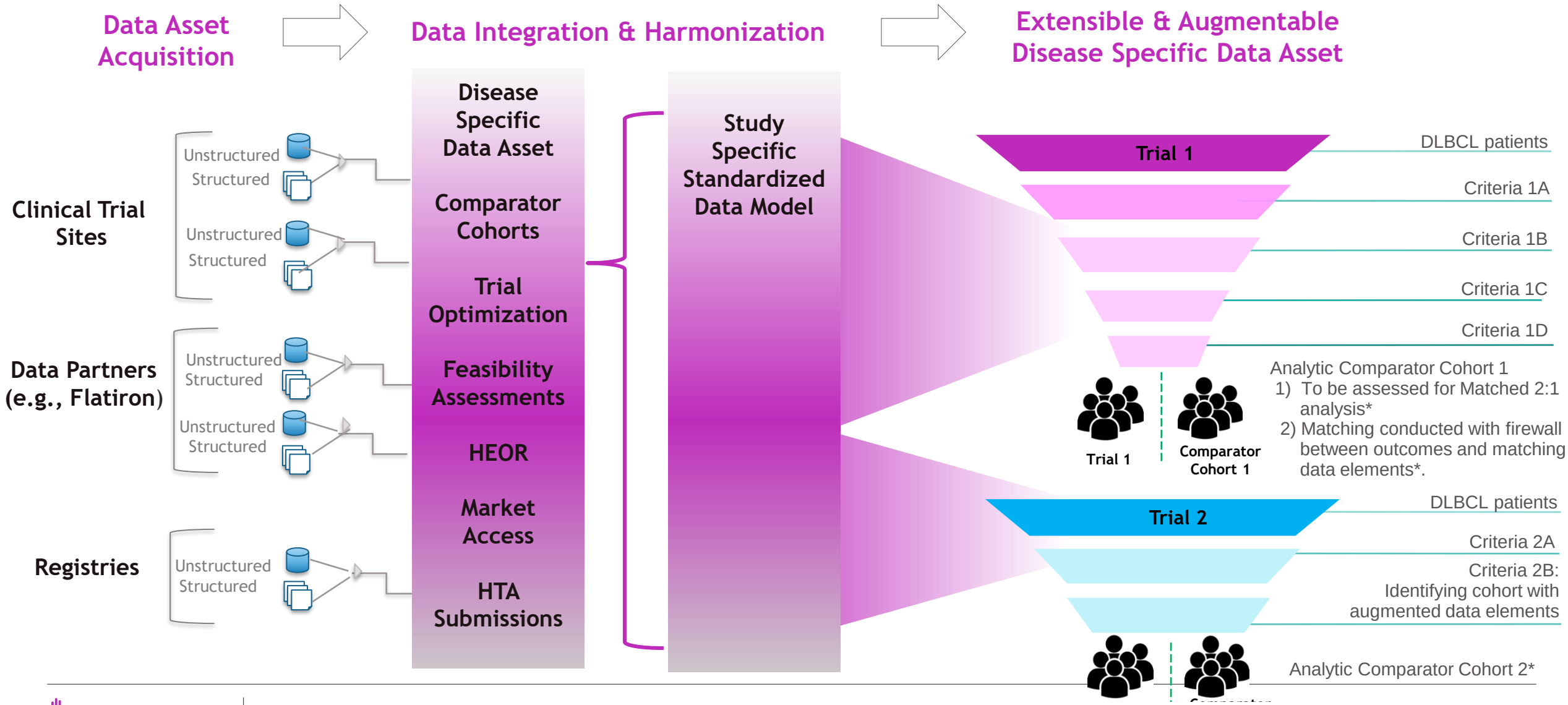
Study design

- Global, non-interventional, retrospective study with RW subjects from a larger cohort with eligibility similar to subjects in TRANSCEND trial; generation of comparator cohort reflecting non-cellular therapy standard of care

- Pre-specified study protocol and SAP for comparison of clinical trial single arm to RWD comparator arm.

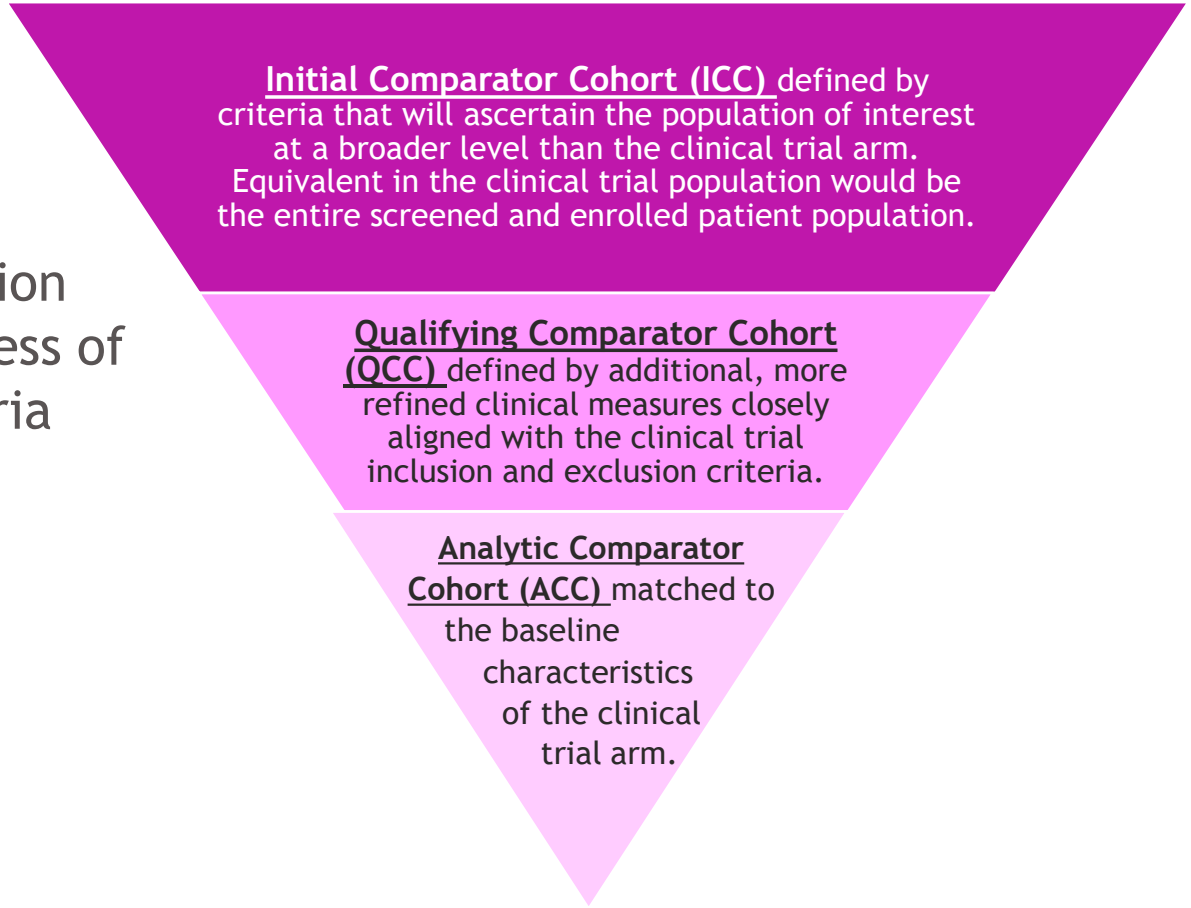


How did we get there? Building Multi-Use RWE Data Assets

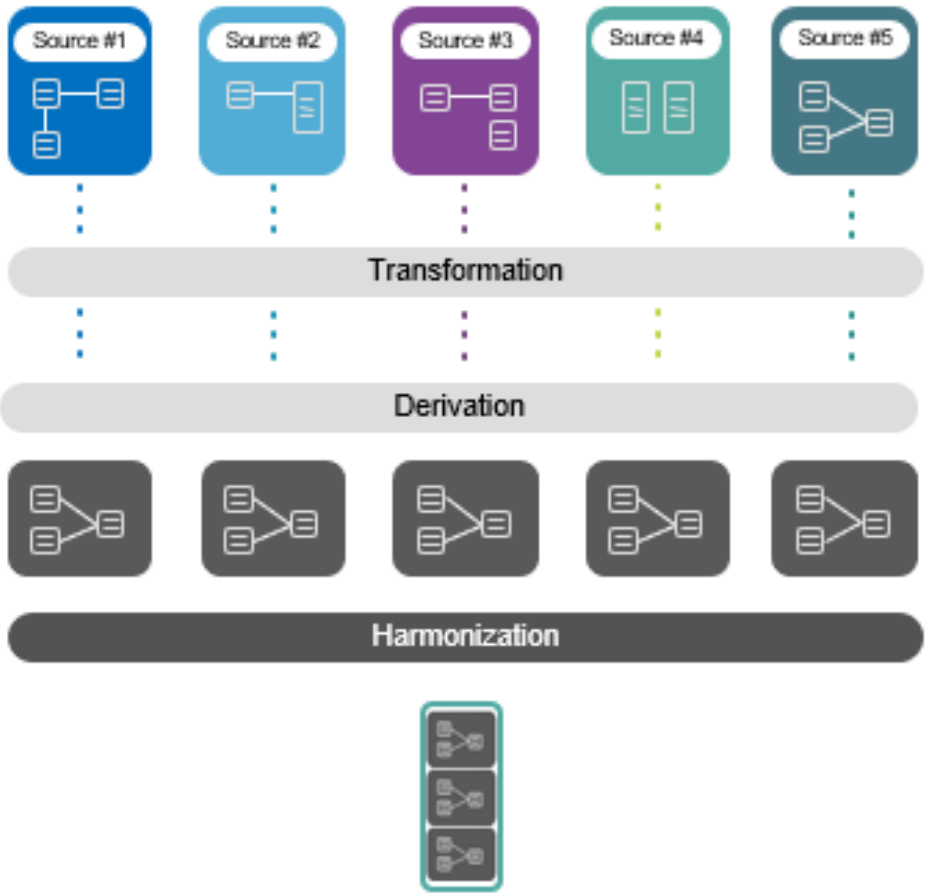


Data Strategy

- Conceptual framework of tiered cohort construction affords ability to understand the representativeness of RWD and details and implications of various criteria filters.



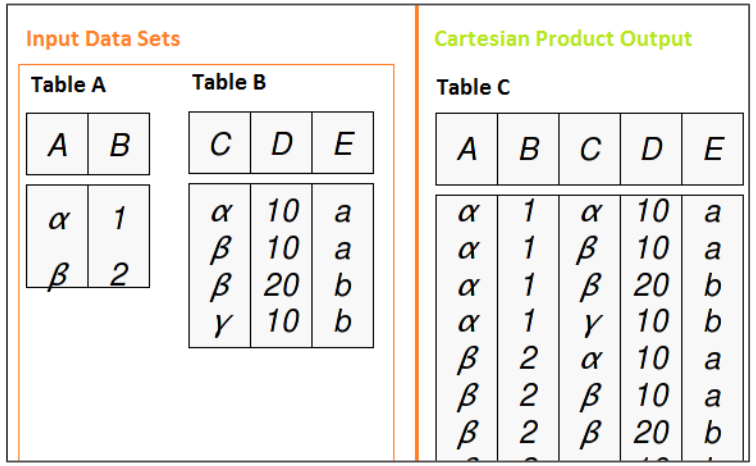
Data Collection and Need for Harmonization: Heterogeneity of RWD Across Data Sources



Data Source	Line of Therapy
Source A	Provider assigned
Source B & C	Not provided
Source D	Derived algorithm – driven by treatment changes
Source E	Derived algorithm - driven by progression & treatment changes

Data Harmonization: De-duplication

- Potential to have duplicate patients in harmonized dataset.
- All patient data de-identified by multiple partners using different methods.
- Three methods developed to identify potential duplicate patients:
  1. Deterministic matching
  2. Probabilistic matching using weighted similarity scores
  3. Probabilistic matching using unweighted similarity scores



Data Harmonization and Clinical Adjudication for Line of Therapy

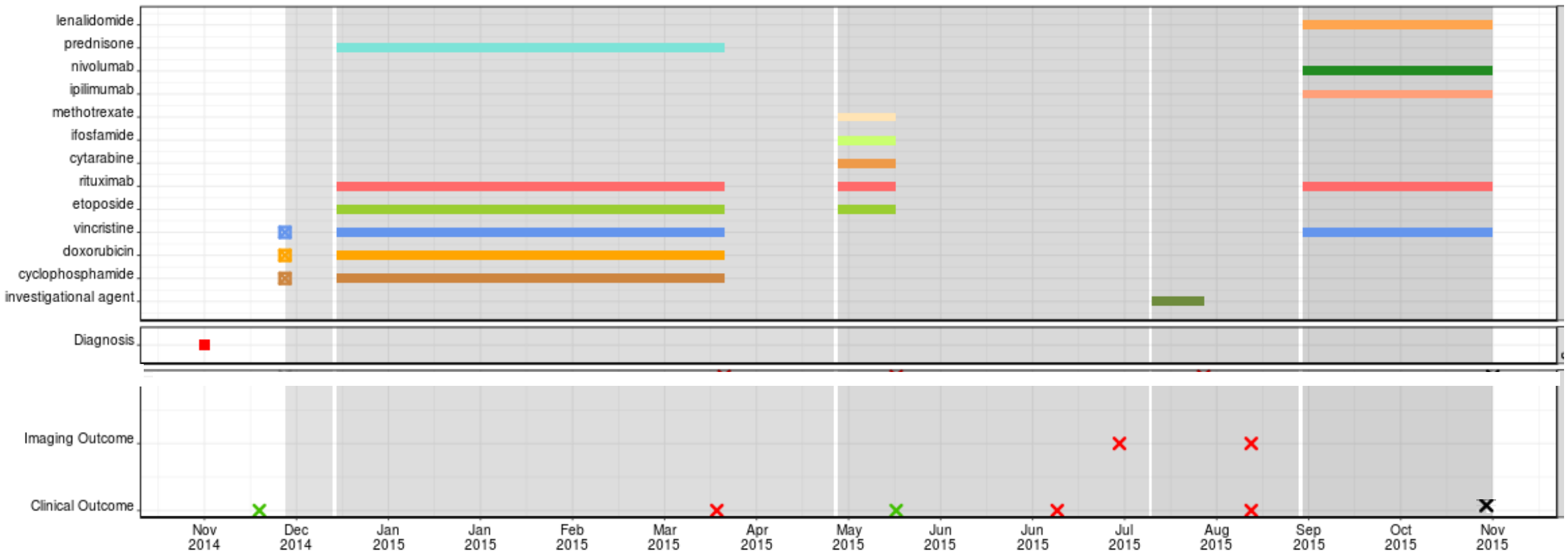
Objectives:

- To derive a programmatic algorithm for assigning treatment line of therapy using RWD for patients with DLBCL.
- To examine the validity of programmatic algorithm compared with a clinical adjudication.

Design:

- 10 Primary Clinical Reviewers and 1 Lead Reviewer
- Provision of guidelines on data structure, definitions, and rules for assignment of LOT.
- 8693 regimens reviewed; 73% (n=6320) underwent a secondary review by Lead Reviewer

Patient Journey



Programmatic LOT Algorithm Hierarchy for 3L+ DLBCL

1. Do not advance line if a stem cell transplant (SCT) within 90 days of previous treatment (s)

Else if

2. Advance line if progression (PD) between start date of treatment and start date of subsequent

Else if

3. Advance line if duration of treatment is less than 30 days and start date of treatment and start date of subsequent treatment is >=90 days.

Else if

4. Do not advance line if no outcome assessment, and end date of treatment and start date of subsequent treatment is < 45 days.

Else if

5. Advance line if no outcome assessment between start date of treatment and start date of subsequent treatment and major change in treatment regimen.

6. Advance line if partial response (PR) between start date of treatment and start date of subsequent treatment and major change in treatment regimen (using reference file or+/- 1 agent not including rituximab.

Else if

7. Do not advance line if duration of treatment is less than 30 days and end date of treatment and start date of subsequent treatment is <90 days.

Else if

8. Advance line if stable disease (SD) between start date of treatment and start date of subsequent

Else if

9. Advance if any above advancement criteria are met.

Impact of Programmatic Hierarchy 3L+ DLBCL on Clinical Adjudication Data Cut

Rule	Action	Hierarchy Rule	N	%
1	No Advance	SCT ≤ 90 days	633	9.8
2	Advance	PD	3057	47.2
3	Advance	Duration < 30 days and ≥ 90 days between start dates	309	4.8
4	No Advance	No response and < 45 days between end date and start date	873	13.5
5	Advance	No response and major change in treatment	122	1.9
6	Advance	PR and major change in treatment	343	5.3
7	No Advance	Duration of treat < 30 days and <90 days between end date and start date	223	3.4
8	Advance	SD	135	2.1
9	Advance	Any of previous advance rules	781	12.1

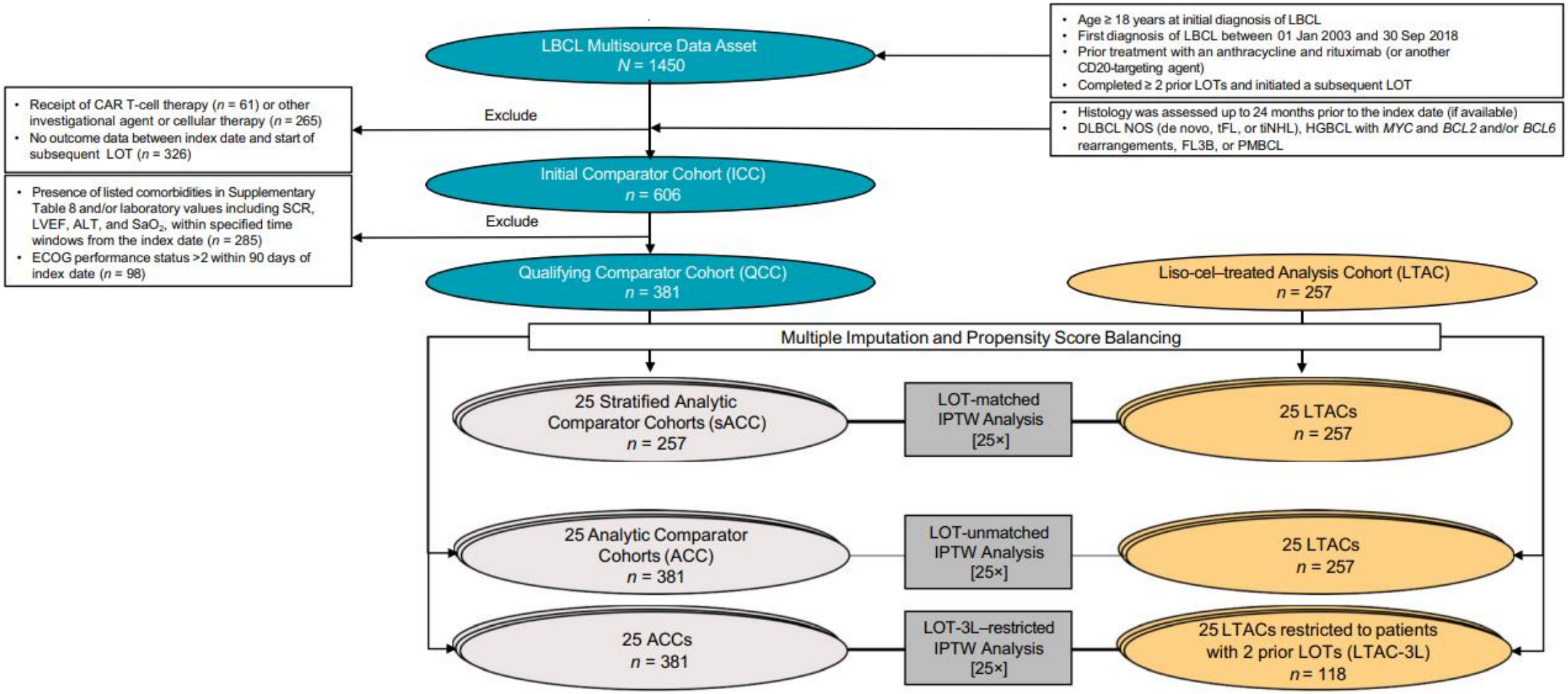
Implications of LOT programmatic algorithm – 3L+ DLBCL

- PPV of clinical adjudication (CA) and programmatic algorithm (PA): 1378/1483 = 93%
- Concordance between CA & PA LOT assignment (regimen level): 6865/8353 = 82%

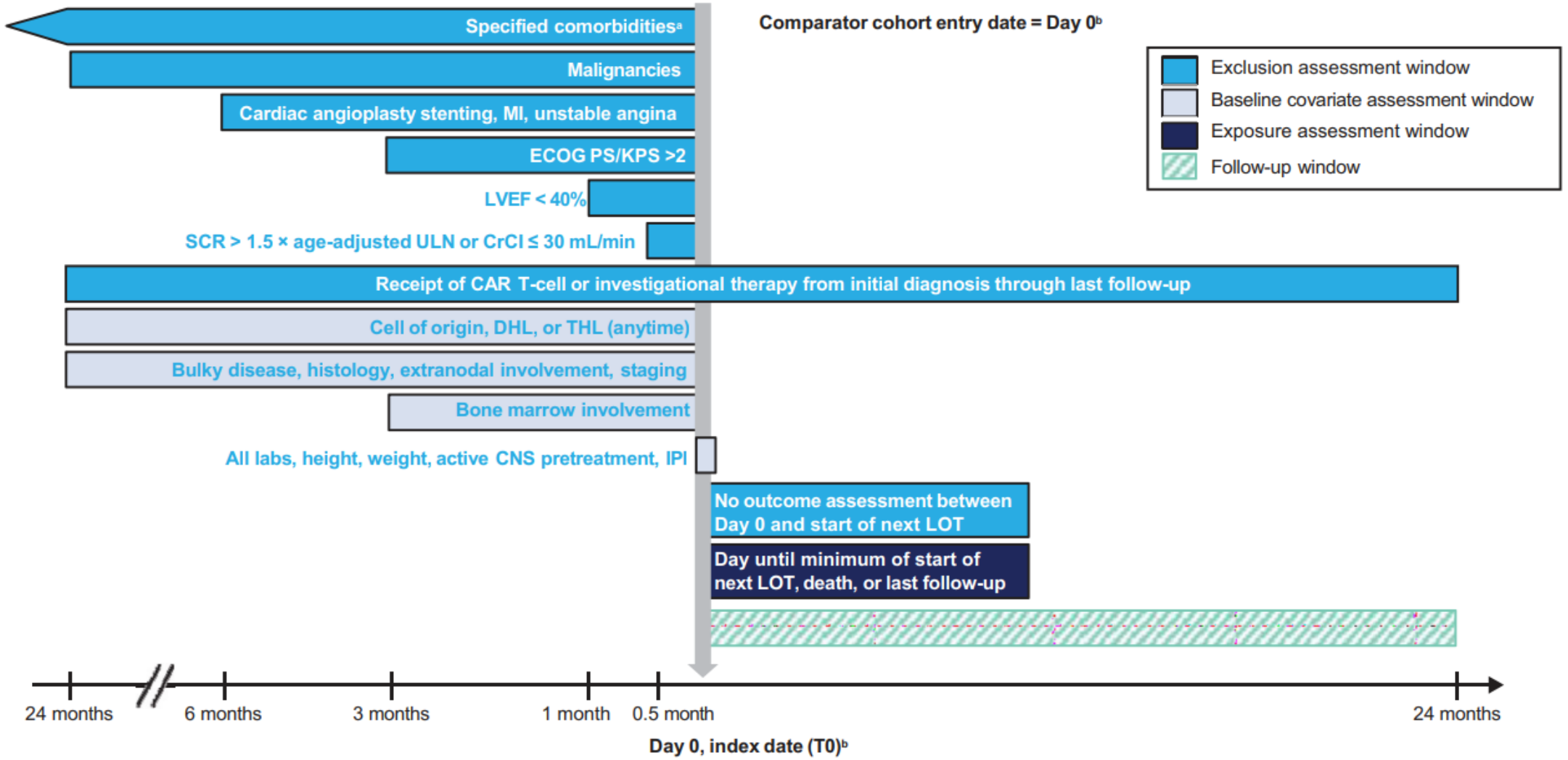
	PROGRAMMATIC ALGORITHM		TOTAL
	1-2 L	3L+	
CLINICAL ADJUDICATION			
1 - 2L	273	105	378
3L+	121	1378	1499
TOTAL	394	1483	1877

Metrics	Total	Source A	Source B	Source C	Source D	Source E
PPV: 1-2L vs. 3L+	93%	87%	100%	93%	95%	93%
Concordance CA & PA regimen level	82%	78%	86%	83%	86%	82%

Comparator cohort attrition



Study design



Challenges with RWD Index Dates

Patient #1

RWD –Retrospective assignment of index date

Patient #1

Clinical trial – Prospective assignment of index date

Stratified Random Assignment of Index Line of Therapy

- Eligibility for the clinical trial occurred prospectively and required DLBCL patients to have received at least 2 LOTs prior to receipt of liso-cel. Thus, patients were enrolled in the clinical trial at 3rd LOT or greater (LOT3+)

- Conversely, eligibility and index LOT for RW patients were defined retrospectively. This assignment of index LOT resulted in a different distribution of prior LOTs in the comparator arm.

Primary and Sensitivity Analyses

Primary Analysis	• Compare sACC (stratified analytic comparator cohort) to LTAC (JCAR017 treated analytic cohort)
Sensitivity 1 (SA1)	• Compare ACC to LTAC
Sensitivity 2 (SA2)	• Compare ACC to a subset of LTAC subjects who received 2 prior LOT
ECOG availability	• Compare pts with ECOG data to LTAC
Patient diagnosed in 2010 or later	• Compare pts diagnosed in 2010 or later to LTAC
EU vs. US RWE Cohorts	• Preliminary/unadjusted analysis comparing EU RWE to US RWE
EU RWE vs. BCM-001	• Preliminary/unadjusted analysis comparing EU RWE to BCM-001 cohort 1

Statistical Analysis

- Study endpoints included
  - Primary: ORR,
  - Secondary: CRR, PFS, OS, DOR and TTR
- Used multiple imputation for missing covariates
- Primary analysis using PS Inverse Probability Treatment Weighting (IPTW) for all primary/secondary endpoints
- Subgroup and sensitivity analyses included enrollment cohorts, matching
- Combined estimates for each endpoint using Rubin's rules
- Used firewall to mask outcome while performing balancing/matching

Analysis Cohorts

Analysis Cohorts	N
Initial Comparator Cohort (ICC)	606
Qualifying Comparator Cohort (QCC)	381
Analytic Comparator Cohort	381
Stratified Comparator Cohort (sACC)	257
JCAR017-treated Analysis Cohort (LTAC)	257
JCAR017-treated Analysis Cohort who received only 2 prior LOTs (LTAC-2L)	118
Leukapheresed Cohort (LKC)	345
Lymphodepleting Chemotherapy Cohort (LDCC)	299

Demographic and Baseline Characteristics

- Comparability between sACC and LTAC on age (median age = 62.0 and 63.0) and sex (63% and 66% males).
- sACC included patients from Europe (30%) while TRANSCEND only US.
- Differences between sACC and LTAC in prior HSCT (18% vs. 34%) and presence of bulky disease (20% vs. 11%).
- Differences in index date assignment in QCC, median number of prior lines and time from initial diagnosis to index date differed.

Prior Lines of Therapy: Primary and Sensitivity Analyses

	Primary Analysis		Sensitivity Analysis 1		Sensitivity Analysis 2	
	sACC (n = 257)	LTAC (n = 257)	QCC (n = 381)	LTAC (n = 257)	QCC (n = 381)	LTAC-2L (n = 118)
No. of prior LOTs						
Median	3.0	3.0	2.0	3.0	2.0	2.0
Min-max	2.0, 4.0	1.0, 8.0	2.0, 2.0	1.0, 8.0	2.0, 2.0	2.0, 2.0
No. of prior LOTs, n (%)						
1	0 (0.0)	9 (3.5)	0 (0.0)	9 (3.5)	0 (0.0)	0 (0.0)
2	127 (49.4)	118 (45.9)	381 (100.0)	118 (45.9)	381 (100.0)	118 (100.0)
3	67 (26.1)	67 (26.1)	0 (0.0)	67 (26.1)	0 (0.0)	0 (0.0)
4	63 (24.5)	39 (15.2)	0 (0.0)	39 (15.2)	0 (0.0)	0 (0.0)
5	0 (0.0)	11 (4.3)	0 (0.0)	11 (4.3)	0 (0.0)	0 (0.0)
6	0 (0.0)	2 (0.8)	0 (0.0)	2 (0.8)	0 (0.0)	0 (0.0)
≥7	0 (0.0)	11 (4.3)	0 (0.0)	11 (4.3)	0 (0.0)	0 (0.0)

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Covariate Balance

Covariate	Before Balancing			After Balancing		
	sACC) (N=257)	LTAC (N=257)	Standardized Mean Difference (LTAC-sACC)	sACC (N=257)	LTAC (N=257)	Standardized Mean Difference (LTAC-sACC)
Age, mean, y	60.98	60.25	-0.0535	60.50	60.36	-0.0101
Sex (male = 1; female = 0)	0.63	0.66	0.0569	0.66	0.65	-0.0129
Months since Diagnosis to Index Date	25.96	31.26	0.1664	27.71	28.43	0.0239
Number of Prior Lines of Therapy	2.75	2.92	0.1497	2.82	2.83	0.0101
Number of Prior LOTs per Year since Diagnosis	2.20	2.23	0.0208	2.22	2.23	0.0078
Best response to any prior therapy (PR/CR = 1,PD/SD =0)	0.69	0.86	0.4260	0.78	0.79	0.0054
Relapsed or Refractory to Last Therapy (Refractory=1,Relapsed=0)	0.93	0.79	-0.3883	0.86	0.86	-0.0070
Prior Hematopoietic Stem Cell Transplant (Yes=1, No=0)	0.18	0.34	0.3808	0.27	0.26	-0.0130
Chemorefractory or Chemosensitive Disease Type (Chemosensitive=1, Relapse< 12 months after ASCT/Last Chemo=0)	0.26	0.33	0.1748	0.30	0.30	-0.0090
Bulky Disease [a] (Yes=1, No=0)	0.20	0.11	-0.2334	0.16	0.16	0.0178
Extranodal Disease (Yes=1, No=0)	0.60	0.53	-0.1425	0.57	0.57	0.0135
Disease Stage (1/2=1, 3/4=0)	0.27	0.27	-0.0038	0.26	0.26	-0.0021

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Overall Effectiveness Results, Adjusted for Stabilized IPTW of RW and JCAR017-treated Analysis Cohorts, Primary and Sensitivity Analyses

End Point	Primary Analysis			Sensitivity Analysis 1			Sensitivity Analysis 2		
	Estimate		RR (95% CI), P value	Estimate		RR (95% CI), P value	Estimate		RR (95% CI), P value
	sACC (n = 257)	LTAC (n = 257)		ACC (n = 381)	LTAC (n = 257)		ACC (n = 381)	LTAC-2L (n = 118)	
ORR, %	38.8	73.8	1.9 (1.6-2.3), <0.0001	38.9	74.7	1.9 (1.6-2.3), <0.0001	39.6	76.1	1.9 (1.6-2.3), <0.0001
CR rate, %	24.1	50.1	2.1 (1.6-2.8), <0.0001	20.4	49.9	2.4 (1.9-3.2), <0.0001	20.7	52.0	2.5 (1.9-3.4), <0.0001
			HR (95% CI), P value			HR (95% CI), P value			HR (95% CI), P value
Median DOR, mo	9.8	10.4	0.79 (0.45-1.37), 0.3938	6.6	10.6	0.80 (0.57-1.13), 0.2079	7.6	16.8	0.80 (0.51-1.26), 0.3387
Median PFS, mo	2.2	3.5	0.60 (0.48-0.75), <0.0001	2.3	3.5	0.58 (0.46-0.72), 0.0001	2.5	4.4	0.57 (0.42-0.77), <0.0003
Median OS, mo	6.8	23.5	0.52 (0.40-0.68), <0.0001	7.9	NR	0.53 (0.41-0.69), <0.0001	8.0	NR	0.45 (0.31-0.65), <0.0001

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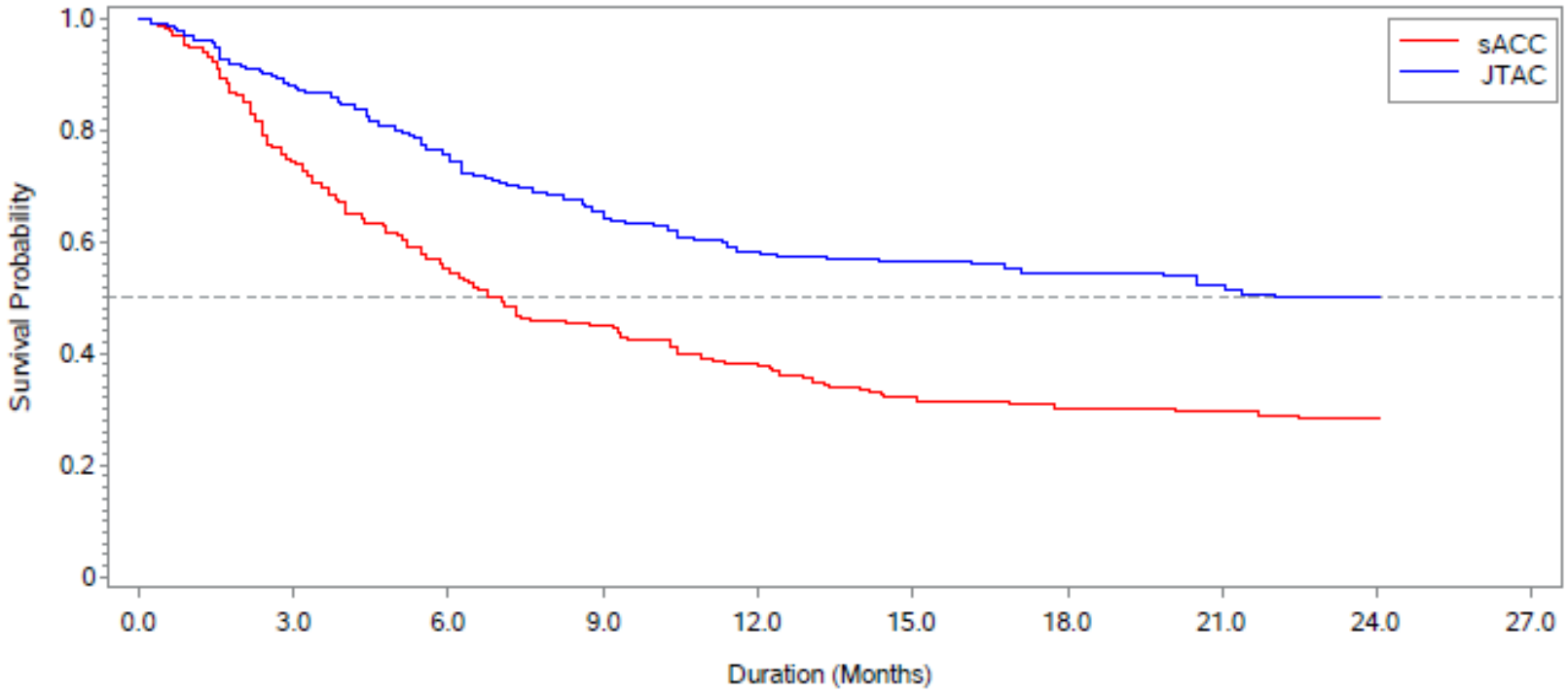
Median DOR, mo	9.8	10.4	0.79 (0.45-1.37), 0.3938	6.6	10.6	0.80 (0.57-1.13), 0.2079	7.6	16.8	0.80 (0.51-1.26), 0.3387
Median PFS, mo	2.2	3.5	0.60 (0.48-0.75), <0.0001	2.3	3.5	0.58 (0.46-0.72), 0.0001	2.5	4.4	0.57 (0.42-0.77), <0.0003
Median OS, mo	6.8	23.5	0.52 (0.40-0.68), <0.0001	7.9	NR	0.53 (0.41-0.69), <0.0001	8.0	NR	0.45 (0.31-0.65), <0.0001

Overall Effectiveness Results, Adjusted for Stabilized IPTW of RW and JCAR017-treated Analysis Cohorts, Primary and Sensitivity Analyses

End Point	Primary Analysis			Sensitivity Analysis 1			Sensitivity Analysis 2		
	Estimate		RR (95% CI), P value	Estimate		RR (95% CI), P value	Estimate		RR (95% CI), P value
	sACC (n = 257)	LTAC (n = 257)		ACC (n = 381)	LTAC (n = 257)		ACC (n = 381)	LTAC-2L (n = 118)	
ORR, %	38.8	73.8	1.9 (1.6-2.3), <0.0001	38.9	74.7	1.9 (1.6-2.3), <0.0001	39.6	76.1	1.9 (1.6-2.3), <0.0001
CR rate, %	24.1	50.1	2.1 (1.6-2.8), <0.0001	20.4	49.9	2.4 (1.9-3.2), <0.0001	20.7	52.0	2.5 (1.9-3.4), <0.0001
			HR (95% CI), P value			HR (95% CI), P value			HR (95% CI), P value
Median DOR, mo	9.8	10.4	0.79 (0.45-1.37), 0.3938	6.6	10.6	0.80 (0.57-1.13), 0.2079	7.6	16.8	0.80 (0.51-1.26), 0.3387
Median PFS, mo	2.2	3.5	0.60 (0.48-0.75), <0.0001	2.3	3.5	0.58 (0.46-0.72), 0.0001	2.5	4.4	0.57 (0.42-0.77), <0.0003
Median OS, mo	6.8	23.5	0.52 (0.40-0.68), <0.0001	7.9	NR	0.53 (0.41-0.69), <0.0001	8.0	NR	0.45 (0.31-0.65), <0.0001

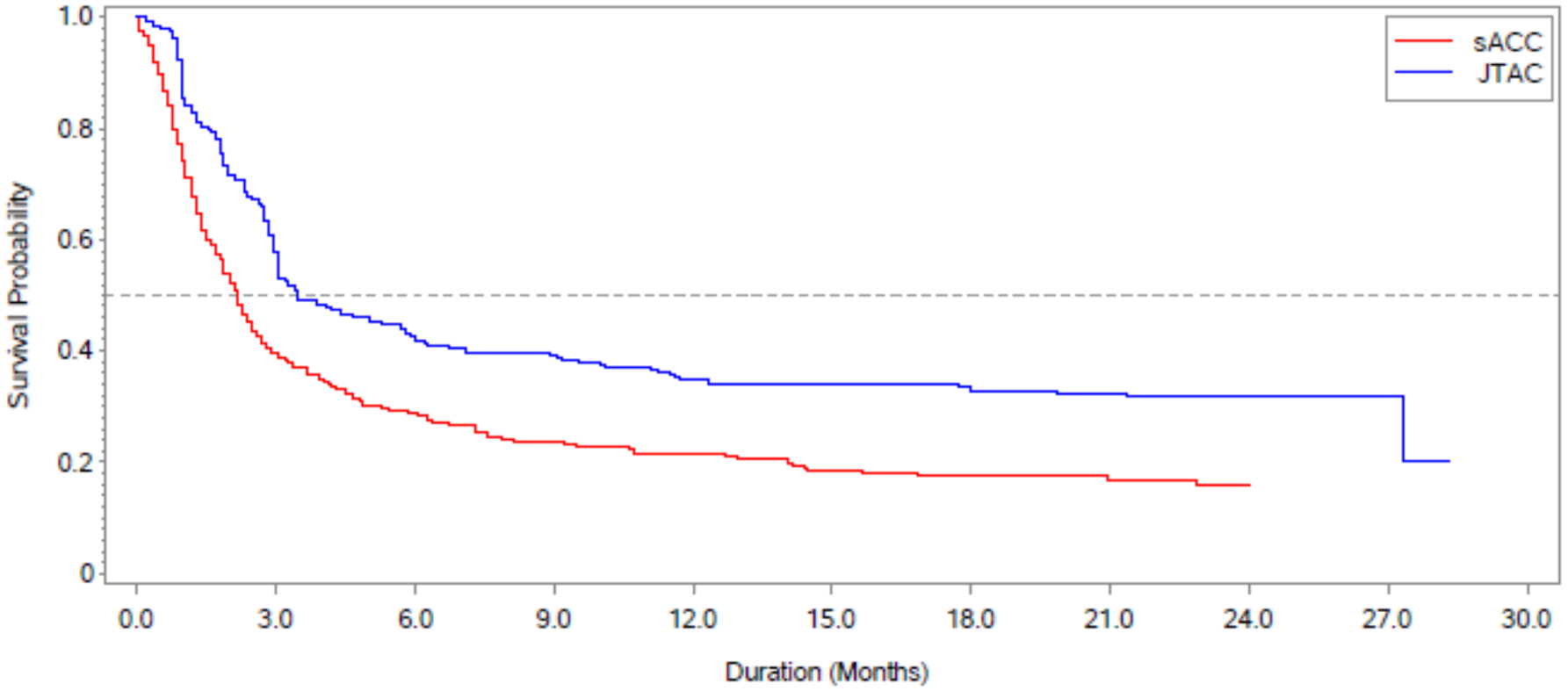
Overall Survival (sACC vs LTAC)



- After median follow-up times of 24.0 months in the LTAC and 17.9 months in the sACC for all surviving subjects, 52.2% of subjects and 36.7% of patients, respectively, were alive

- The median OS was statistically significantly longer in the LTAC as compared with the sACC (23.5 months versus 6.8 months; p = 0.0001

Progression Free Survival - (sACC vs. LTAC)



- After median follow-up times of 10.6 months in the LTAC and 6.5 months in the sACC for all surviving subjects, 32.3%% of LTAC subjects and 19.1% of sACC patients, respectively, were progression free.

- The median PFS was statistically significantly longer in the LTAC as compared with the sACC (3.5 months versus 2.3 months; p = 0.0001

Discussion/Conclusion

- This study confirms the high unmet medical need for patients with 3L+ R/R LBCL.
- Assignment methods of index LOTs impacted the median overall survival in RW.
- Significantly improved outcomes were demonstrated with liso-cel treatment in the TRANSCEND cohort vs similar RW cohort.
- These findings support the conclusion that liso-cel provides significant and meaningful benefit for patients with 3L+ R/R LBCL relative to available therapies.

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