Proportional Randomization Method to Identify Index Line of Therapy in Externally Controlled Trials

MSR105

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Background

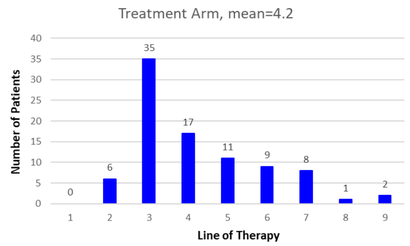
- In some externally controlled trials (ECT), patients in the treatment arm receive the investigational drug in different lines of therapy (index LOTs), and the index LOTs for patients in the external control arm (ECA) are to be determined.[1]
- Random selection of LOT is often used to identify index LOT.[2, 3]
- Most existing methods to determine index LOT fail to balance LOT distribution between the two arms.
- **Objective**: This study proposes and validates a new method to identify index LOT for patients in the ECA based on the known index LOT distribution from the treatment arm.

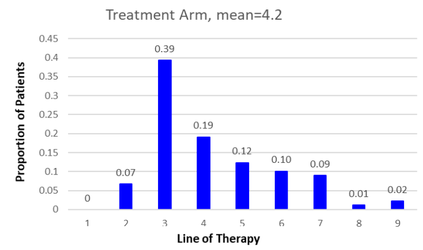
Methods

- We proposed a proportional randomization algorithm to assign patients from the ECA into a frequency distribution similar to the index LOTs of patients in the treatment arm.
- The index LOT for a patient from the ECA is then defined as one of the available eligible LOTs closest to the assigned LOT in the distribution.
- This LOT assignment was initially assessed by comparing the LOT distributions between the two arms and further validated by assessing the stability and variability of the standardized mean differences (SMD) from 1000 proportional randomization samples. An SMD≤0.1 is considered balance in LOT between the two arms.
- In a case study of ECT with single arm trial **BRUIN-18001** and real-word **ConcertAI** Oncology Dataset for mantle cell lymphoma (MCL), the index LOT frequency distribution was obtained from BRUIN and applied in the proportional randomization method to identify index LOT for patients from ConcertAI data.

Methods

Step 1: Obtain Treatment Arm LOT Distribution. Calculate the proportion and interval of the proportion for each LOT.



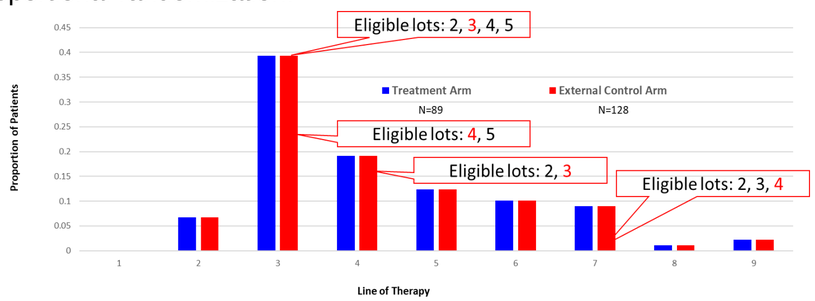


Step 2: Conduct Proportional Randomization. Randomly assign patients from the ECA into a frequency distribution proportional to that of the index LOTs of patients in the treatment arm.

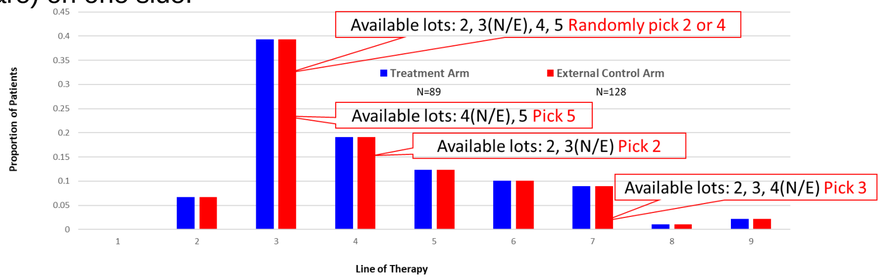
Treatment Arm LOT	1	2	3	4	5	6	7	8	9
Proportion	0.00	0.07	0.39	0.19	0.12	0.10	0.09	0.01	0.02
Cumulation	0.00	0.07	0.46	0.65	0.78	0.88	0.97	0.98	1.00
Interval	[0.00, 0.00]	(0.00, 0.07]	(0.07, 0.46]	(0.46, 0.65]	(0.650, 0.78]	(0.78, 0.88]	(0.88, 0.97]	(0.97, 0.98]	(0.98, 1.00]

ECA Patient ID	Random number
1	.90466
5	.26243
6	.25167
7	.53713
8	.82865
10	.11706
13	.60121
16	.77570
18	.24663
19	.33642
.....	.....

Step 3: Identify ECA index LOT. Define the index LOT for a patient from the ECA as one of the available eligible LOTs closest to the assigned LOT in Step 2 using proportional randomization.

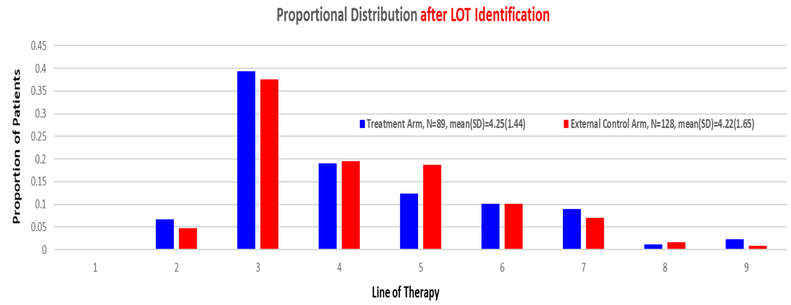


Step 4: Address Special Cases. In special cases that the best available LOT is still not eligible (N/E), such as a LOT containing CAR-T or a clinical study drug, a simple randomization will be conducted to choose one eligible LOT on either side, or the next best available LOT will be selected if other available LOT(s) is (are) on one side.



Methods

Step 5: Validation. This LOT assignment was initially assessed by comparing the LOT distributions between the two arms and further validated by assessing the stability and variability of the standardized mean differences (SMD) from 1000 proportional randomization samples.



Results

- The proportional randomization method used all the eligible patients in the ECA (no loss of sample size).
- The proportional randomization method produced a frequency distribution of index LOTs for real-world patients similar to that for BRUIN patients (mean (SD)=4.25(1.44) vs 4.22(1.65), two-sided t-test p-value=0.91, SMD=0.016).
- The mean and 95% confidence interval of SMDs based on the 1000 proportional randomization samples were 0.035(0.001, 0.093).
- The LOT differences between the two arms are minimal.

Conclusions

- The proportional randomization method was successfully used to identify index LOT in this ECT, and its applicability can be explored in future ECTs.

REFERENCES

1. FDA Draft Guidance: Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products Guidance for Industry. February 2023.
2. Chen, Y., Martin, P., Ye, S., Inoue, L., Basu, A., & Carlson, J. J. (2023). RWD19 Comparative Effectiveness Using External Controls for Single-Arm Trials of Pembrolizumab in Tumor-Agnostic Indications Leveraging Real-World Data. Value in Health, 26(6), S363-S364.
3. Velummailum, R. R., McKibbon, C., Brenner, D. R., Stringer, E. A., Ekstrom, L., & Dron, L. (2023). Data challenges for externally controlled trials. Journal of Medical Internet Research, 25, e43484.

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