Survival of the Fittest: Digitising Survival Data for Enhanced Decision-Making in Clinical Trials

James Sykes and Nelson Kinnersley

Content

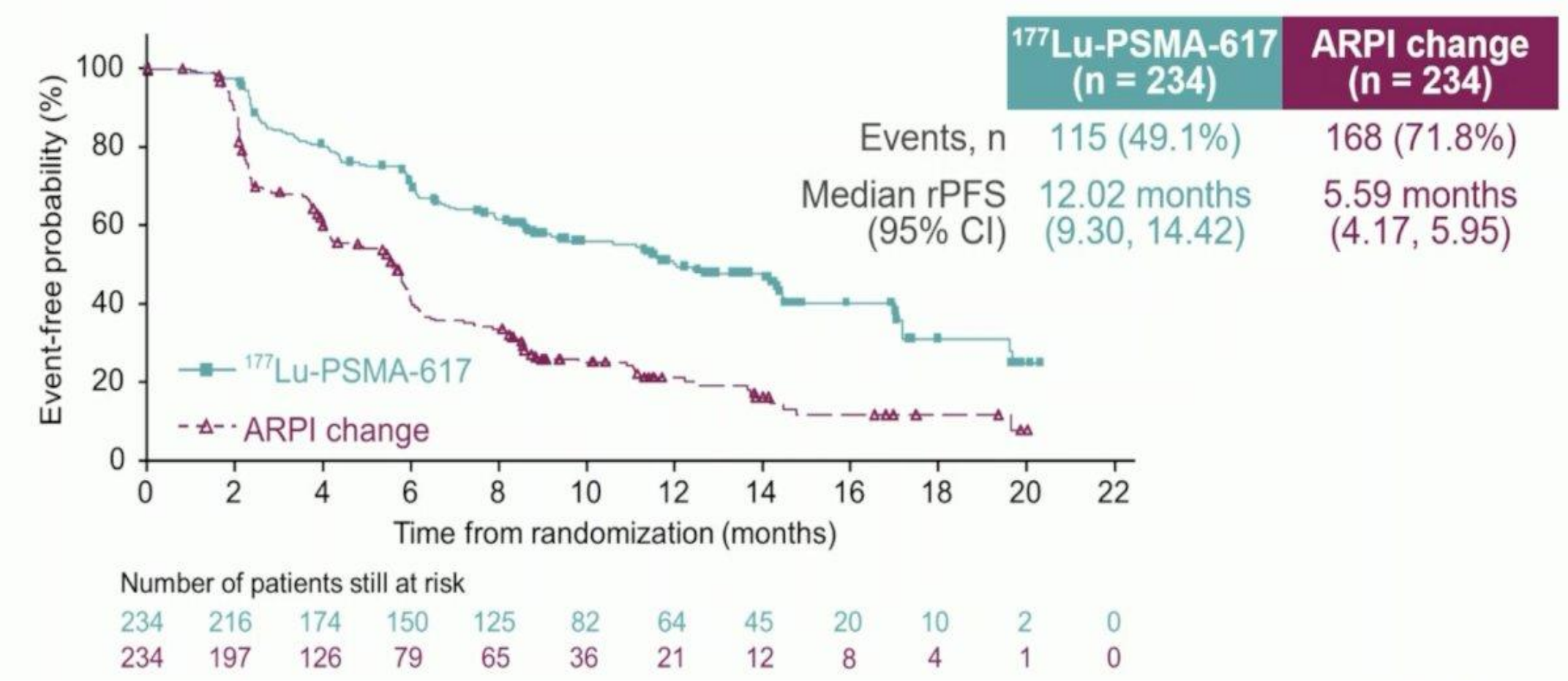
- Traditional Approaches to Modelling Survival Data Using a Historical Control
- Digitising survival data – how do we do that?
- Case Study #1 – Non-Oncology
- Case Study #2 – Oncology
- Conclusions

- By the end of the presentation, we hope the audience understand:
  - What digitising survival data is and how it can be performed
  - How digitised data could be used in a clinical trial setting for decision making
  - Some of the benefits and limitations of using such data

Traditional Approaches to Modelling Survival Data Using a Historical Control

- Last year, Nelson and I were asked the following question by the CMO of Blue Earth Therapeutics:
  - *12 months after the first subject dosed in Phase 2, to what extent will we be able to benchmark radiographic progression-free survival (rPFS) vs our competitor?*
  - *We have the Kaplan-Meier for the comparator trial, and we know that median rPFS is approximately 12 months.*
  - *Would it be possible to set "futility" and "efficacy" criteria to action Phase 3 at the 12-month point based on the number of rPFS events? E.g. if at 12 months we see 30 events, this is a much higher rate than our competitor which means we hit futility. If, for example, we only have 5 progression events then we are someway ahead.*

Traditional Approaches to Modelling Survival Data Using a Historical Control

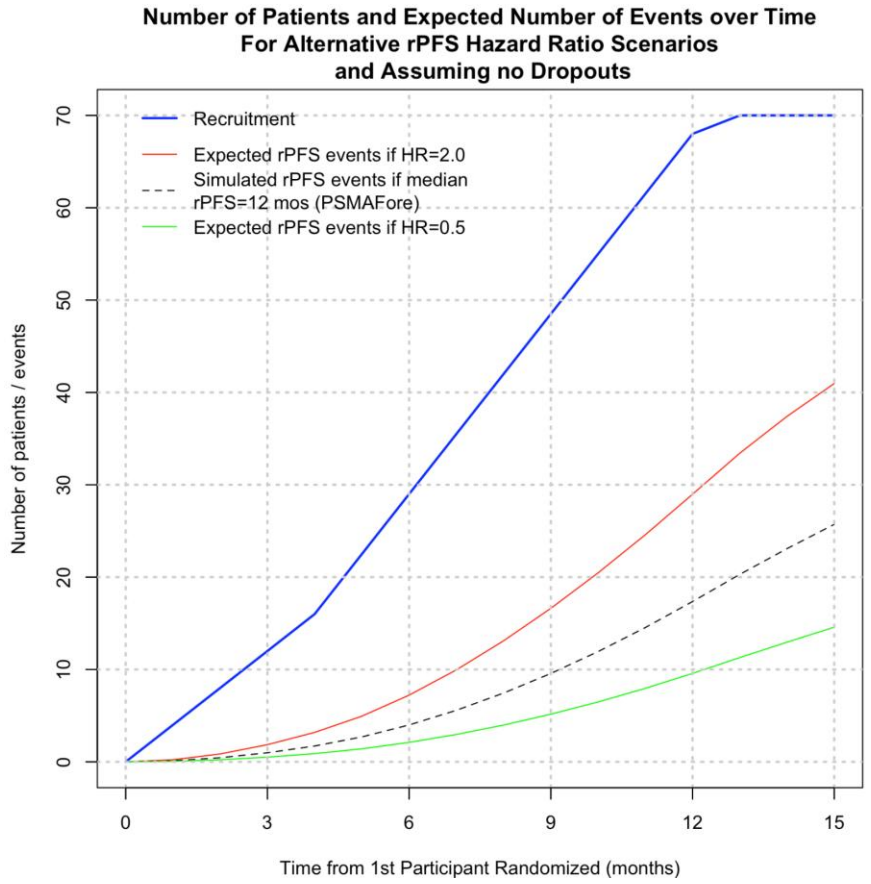


https://www.urotoday.com/conference-highlights/esmo-2023/esmo-2023-prostate-cancer/147587-esmo-2023-psmafore-phase-3-trial-of-177lu-lu-psma-617-in-taxane-naive-patients-with-mcrpc.html

Traditional Approaches to Modelling Survival Data Using a Historical Control

- Our approach was to assume an exponential model fit for the published KM curve and then perform event predictions in R.
- *Working assumptions*
  - *Staggered enrolment of all 70 patients in 12 months*
  - *Assumed futility criteria: Hazard Ratio = 2.0*
  - *Assumed efficacy criteria: Hazard Ratio = 0.5*
  - *We produced a model-based exponential distribution with median PFS=12 to replicate the competitor*
  - *Event predictions per month for a HR of 2.0*
  - *Event predictions per month for a HR of 0.5*

Traditional Approaches to Modelling Survival Data Using a Historical Control



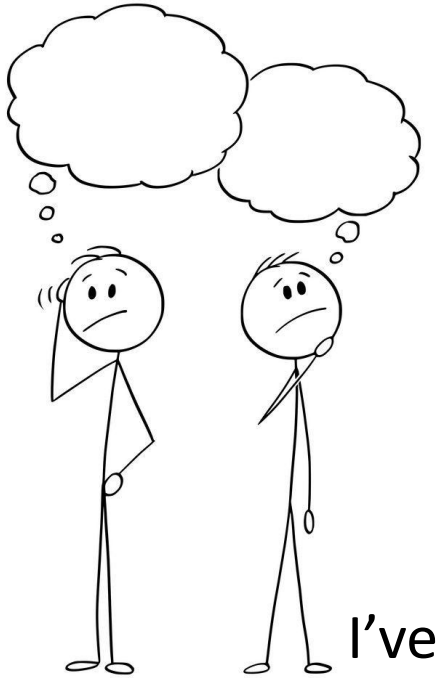
Number of Patients and Expected Number of Events over Time For Alternative rPFS Hazard Ratio Scenarios and Assuming no Dropouts

Time	Recruitment	Expected rPFS events if HR=2.0	Simulated rPFS events if median rPFS=12 mos (PSMAFore)	Expected rPFS events if HR=0.5
0	0.0	0.0	0.0	0.0
1	4.0	0.2	0.1	0.1
2	8.0	0.9	0.4	0.2
3	12.0	1.9	1.0	0.5
4	16.0	3.2	1.7	0.9
5	22.5	4.9	2.7	1.4
6	29.0	7.2	4.0	2.1
7	35.5	10.0	5.6	3.0
8	42.0	13.1	7.4	4.0
9	48.5	16.6	9.6	5.2
10	55.0	20.5	11.9	6.5
11	61.5	24.6	14.5	8.0
12	68.0	29.0	17.4	9.6
13	70.0	33.4	20.3	11.3
14	70.0	37.4	23.1	13.0
15	70.0	41.0	25.7	14.6

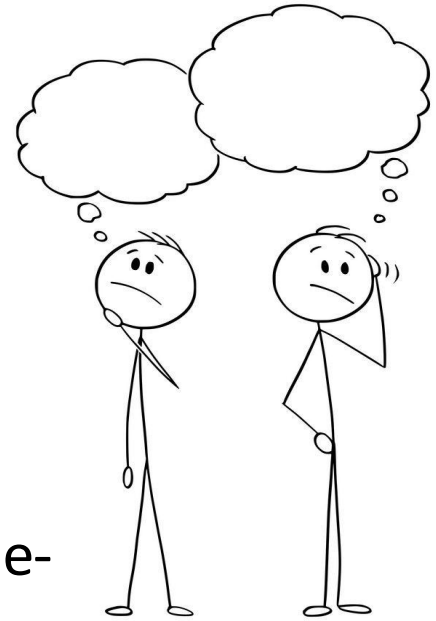
- Based on this approach, we could set futility/efficacy criteria at 29/10 events to inform internal decision making at 12 months.
- Created using RPACT R package (see references)

Traditional Approaches to Modelling Survival Data

How could we improve on our approach?



Could we get hold of the individual patient data?



I've heard you can digitise survival data… Reverse-engineering the IPD might be a useful exercise

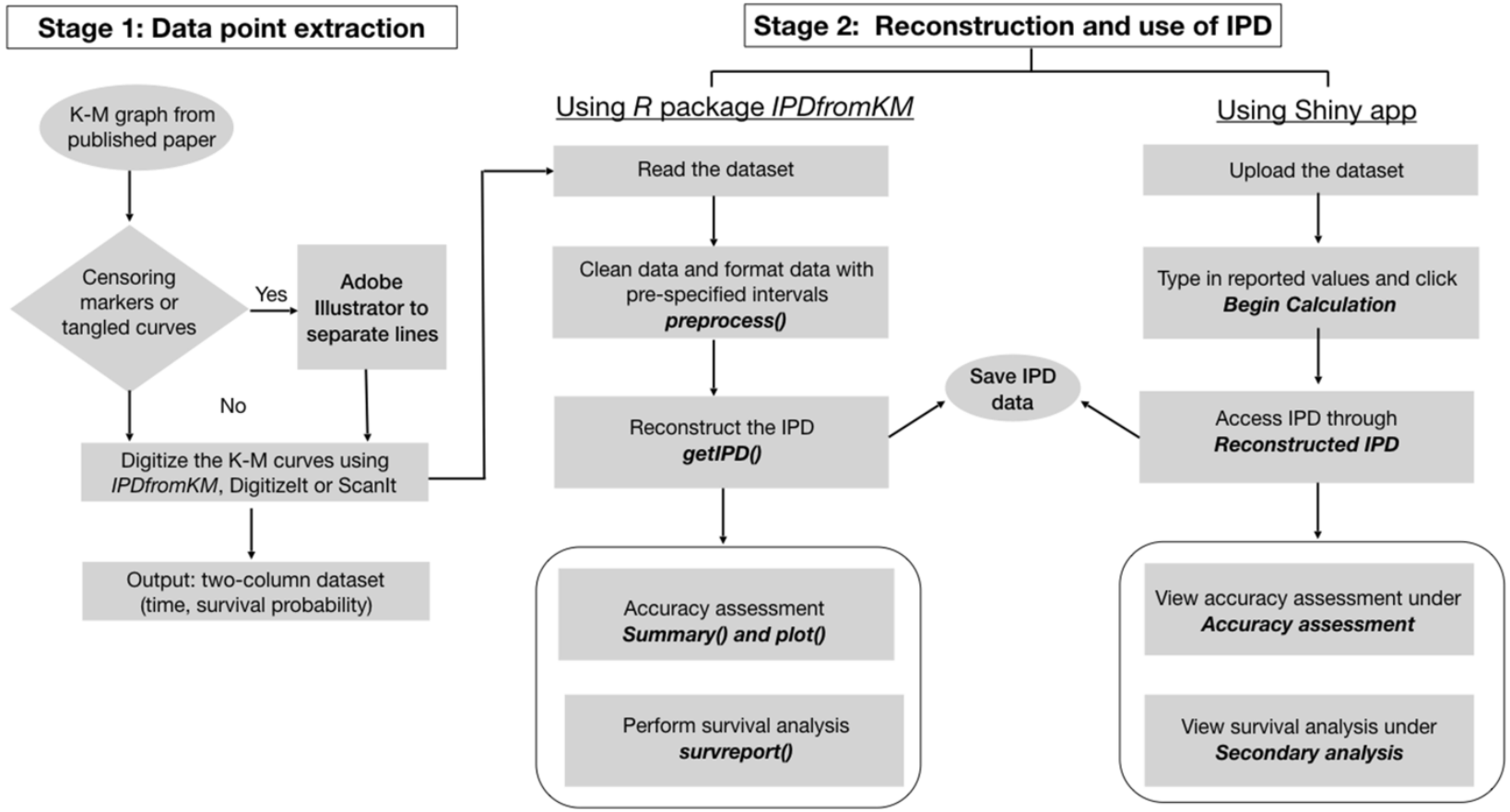
Digitising survival data… How do we do that?

Digitising Survival Data – How Do We Do That?

- In clinical research, access to raw patient-level data is often restricted, making it difficult to perform robust decision-making analyses.
- The IPDfromKM method reconstructs individual patient data (IPD), the gold standard for data analysis, from Kaplan-Meier survival curves. This provides a systematic approach to extracting patient-level survival data.
- Digitization of Kaplan-Meier curves converts graphical survival estimates into numerical values which can be used to compare ongoing research to historical controls.

Digitising Survival Data – How Do We Do That?

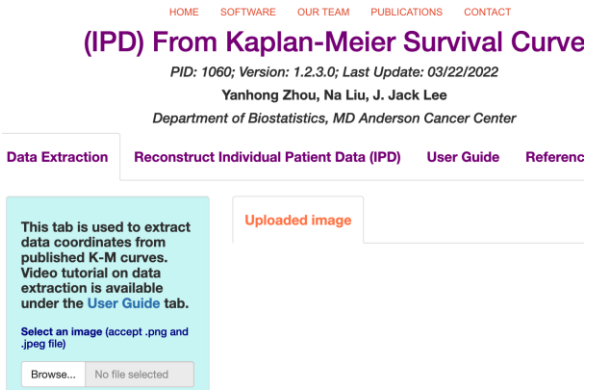
- Stage 1 extracts raw data coordinates and Stage 2 reconstructs IPD using the proposed method.



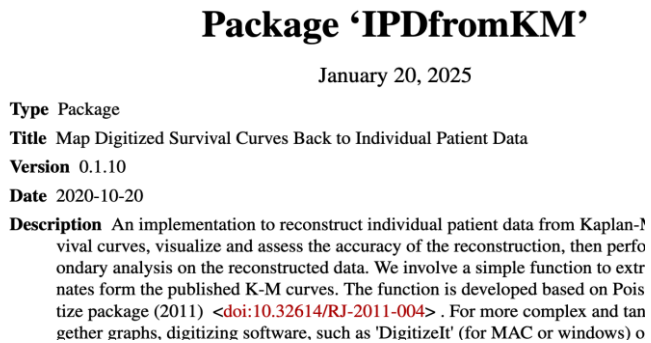
Digitising Survival Data – How Do We Do That?

- Data coordinates can be extracted from K-M curves using the R package and Shiny application
- The IPD reconstruction is carried out using the modified-iKM algorithm, which is based on the K-M estimation method

https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/s12874-021-01308-8



https://trialdesign.org/one-page-shell.html#IPDfromKM



https://cran.r-project.org/web/packages/IPDfromKM/index.html

Case Study #1 – Non-Oncology

Sciurba et al. CHEST (2025) https://journal.chestnet.org/action/showPdf?pii=S0012-3692%2824%2904937-7

[COPD Original Research]

CHEST

Effect of Dual Phosphodiesterase 3 and 4 Inhibitor Ensifentrine on Exacerbation Rate and Risk in Patients With Moderate to Severe COPD

Frank C. Sciurba, MD; Stephanie A. Christenson, MD; Tara Rheault, PhD, MPH; Thomas Bengtsson, MSc; Kathleen Rickard, MD; and Igor Z. Barjaktarevic, MD, PhD

BACKGROUND: Exacerbations in COPD can be life-threatening and can lead to irreversible declines in lung function and quality of life. Medications that reduce exacerbation burden are an unmet need, because exacerbations put patients at risk of more exacerbations and decrease quality of life. Ensifentrine is a first-in-class selective dual inhibitor of phosphodiesterase 3 and 4 with demonstrated nonsteroidal antiinflammatory activity and bronchodilatory effects.

RESEARCH QUESTION: Does ensifentrine reduce the rate or risk of COPD exacerbations?

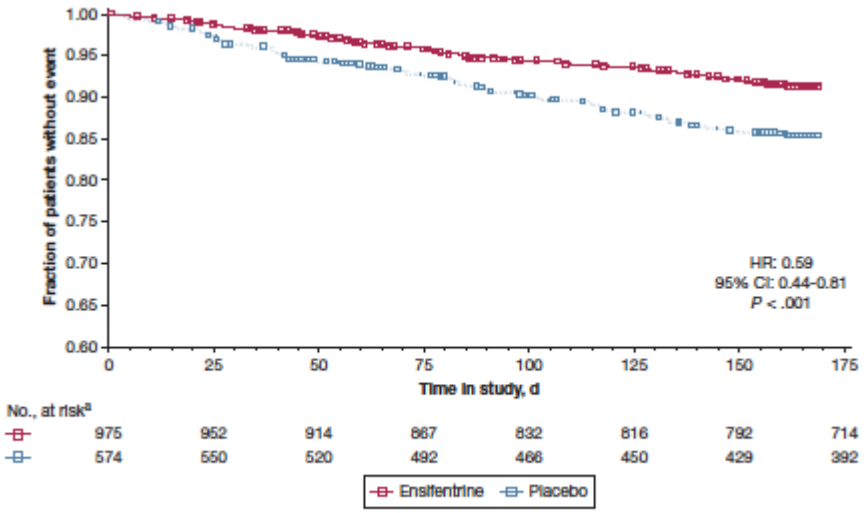
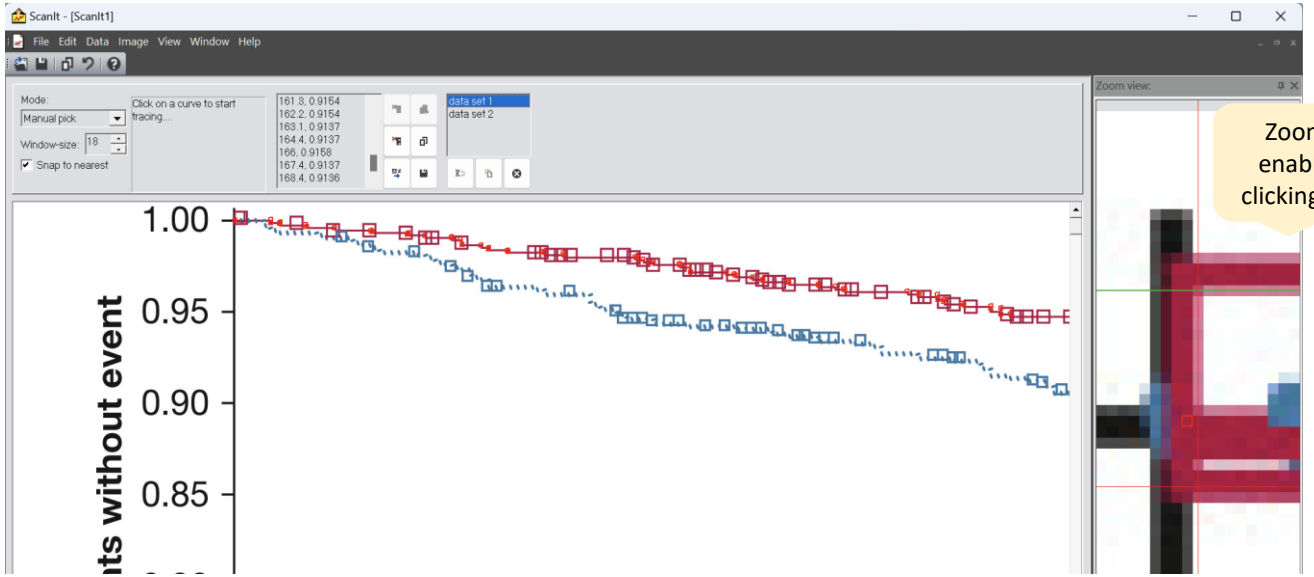


Figure 2 – Kaplan-Meier plot showing time to first moderate to severe COPD exacerbation over 24 weeks. [a]Reported number at risk corresponds to the last exacerbation that occurred during the interval reported. HR = hazard ratio.

Case Study #1 – Non-Oncology



Zoom window enables precise clicking (if desired)

https://www.amsterchem.com/scanit.html

	A	B	C
1	0	1	Arm 1
2	4.006	1	Arm 1
3	4.006	0.9989	Arm 1
4	5.041	0.9993	Arm 1
5	4.972	0.9986	Arm 1
6	7.804	0.9979	Arm 1
7	7.942	0.9968	Arm 1
8	10.98	0.9961	Arm 1
9	14.99	0.9947	Arm 1

106	167.4	0.9137	Arm 1
107	168.4	0.9136	Arm 1
108	0	1	Arm 2
109	3.246	1	Arm 2
110	3.453	0.9975	Arm 2
111	3.936	0.9961	Arm 2
112	4.489	0.9961	Arm 2
113	4.489	0.9947	Arm 2
114	4.972	0.9944	Arm 2
115	8.978	0.9933	Arm 2

Data Extraction | **Reconstruct Individual Patient Data (IPD)**

Number of treatment groups

○ One ◉ Two

Upload a three-column dataset (time, survival probability, treatment indicator) extracted from published K-M curve. Accept .csv and .txt files. Templates: example.csv, example.txt.

Browse... Sciurba_Fig2_arm1_arm2.txt

Upload complete

Risk time (*trisk*) seperated by comma: e.g., 0,6,12,18,24.:

Treatment 1: Arm 1: 0,25,50,75,100,125,150,175

Treatment 2: Arm 2: 0,25,50,75,100,125,150,175

Number of patients at risk (*nrisk*) seperated by comma: e.g., 144,83,45,32,10.:

Treatment 1: Arm 1: 975,952,914,867,832,816,792,714

Treatment 2: Arm 2: 574,550,520,492,466,450,429,392

Total number of patients (optional if *nrisk* is provided)

Treatment 1: Arm 1: 975

Treatment 2: Arm 2: 574

Total number of events (optional):

Treatment 1: Arm 1: 84

Treatment 2: Arm 2: 81

Input required to obtain survival analysis based on reconstructed IPD

Length of time interval (for reporting survival probability)

25

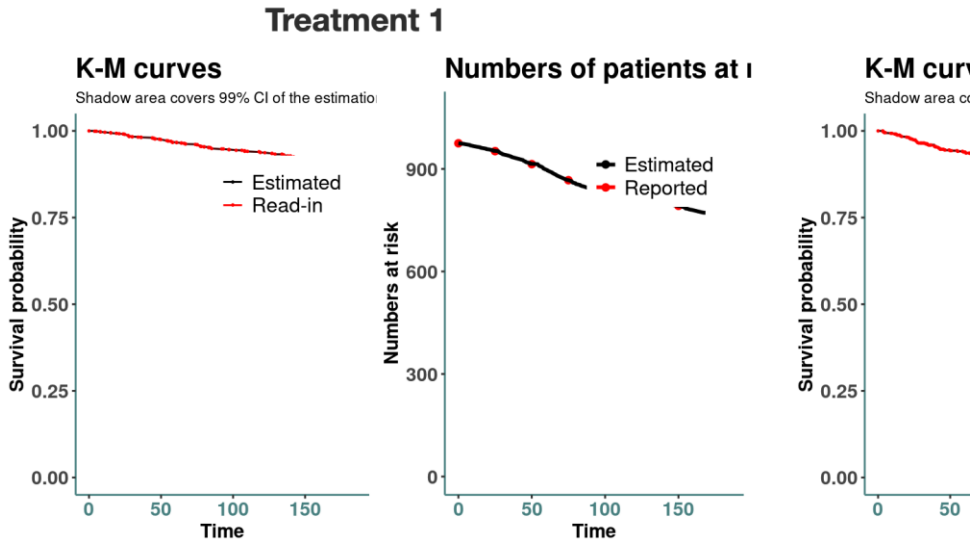
A vector of survival probabilities, for which survival times are of interest (Seperated by comma)

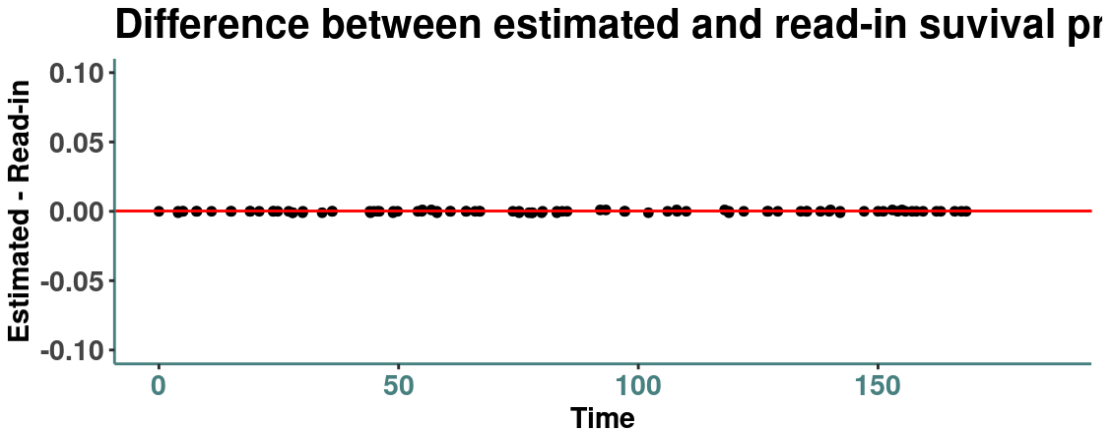
0.85,0.9,0.95

Begin Calculation | Edit

Case Study #1 – Non-Oncology

This panel shows the summary results that assess the accuracy and reproducibility of the modified-iKM algorithm.





Reconstructed IPD | Accuracy assessment | Secondary ana

This panel shows the IPD reconstructed from uploaded dataset. The result can be copy, print, or save by clicking on the following tabs.

Copy CSV Print

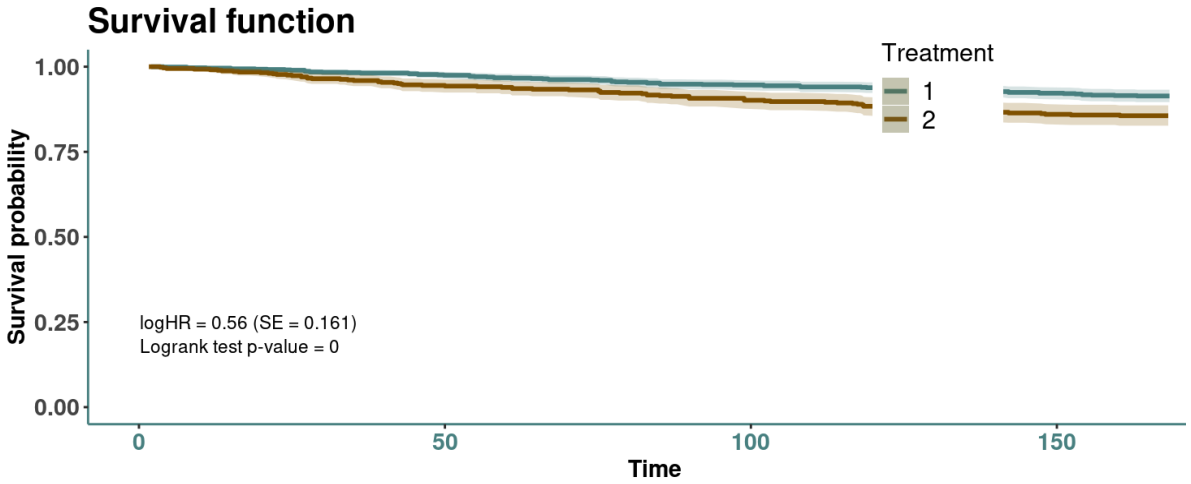
Survival time	Status	Treatment group
2.003	0	Arm 1
2.003	0	Arm 1
4.006	1	Arm 1
6.423	0	Arm 1
6.423	0	Arm 1

Table 1. Accuracy evaluation.

Summary statistics	Treatment 1 (Arm 1)	Treatment 2 (Arm 2)
Root mean square error (RMSE)	0.001	0.001
Mean absolute error	0	0.001
Max absolute error	0.001	0.001
Kolmogorov-Smirnov test statistics (p-value)	0.04(1)	0.03(1)

Case Study #1 – Non-Oncology

This panel shows the K-M curve and cumulative risk for each treatment based on the reconstructed IPD, reports landmark survival probabilities at pre-specified times, and display survival times at given survival probabilities.



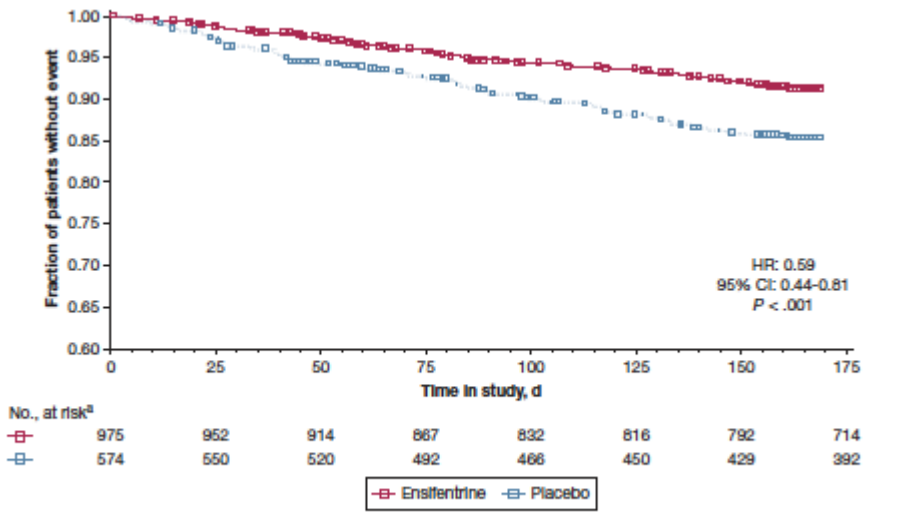


Figure 2 – *Kaplan-Meier plot showing time to first moderate to severe COPD exacerbation over 24 weeks. [a]Reported number at risk corresponds to the last exacerbation that occurred during the interval reported. HR — hazard ratio.*

Table 1. Landmark survival probability, standard error (SE), and 95% condifence interval (CI) given pre-specified time point.

Time	Survival probability	SE	95% lower CI	95% upper CI
Treatment 1 (Arm 1)				
25	0.9897	0.0033	0.9833	0.9961
50	0.9749	0.0051	0.9651	0.9849
75	0.9609	0.0063	0.9486	0.9733
100	0.9464	0.0074	0.932	0.961
125	0.9372	0.008	0.9217	0.953
150	0.9222	0.0089	0.905	0.9398
Treatment 1 (Arm 2)				
25	0.9736	0.0067	0.9605	0.9869
50	0.9431	0.0098	0.9241	0.9624
75	0.9319	0.0107	0.9113	0.9531
100	0.9014	0.0128	0.8767	0.9267
125	0.8818	0.0139	0.855	0.9095
150	0.8601	0.015	0.8311	0.89

Table 2. Survival times and 95% condifence interval (CI) given pre-specified survival probabilities.

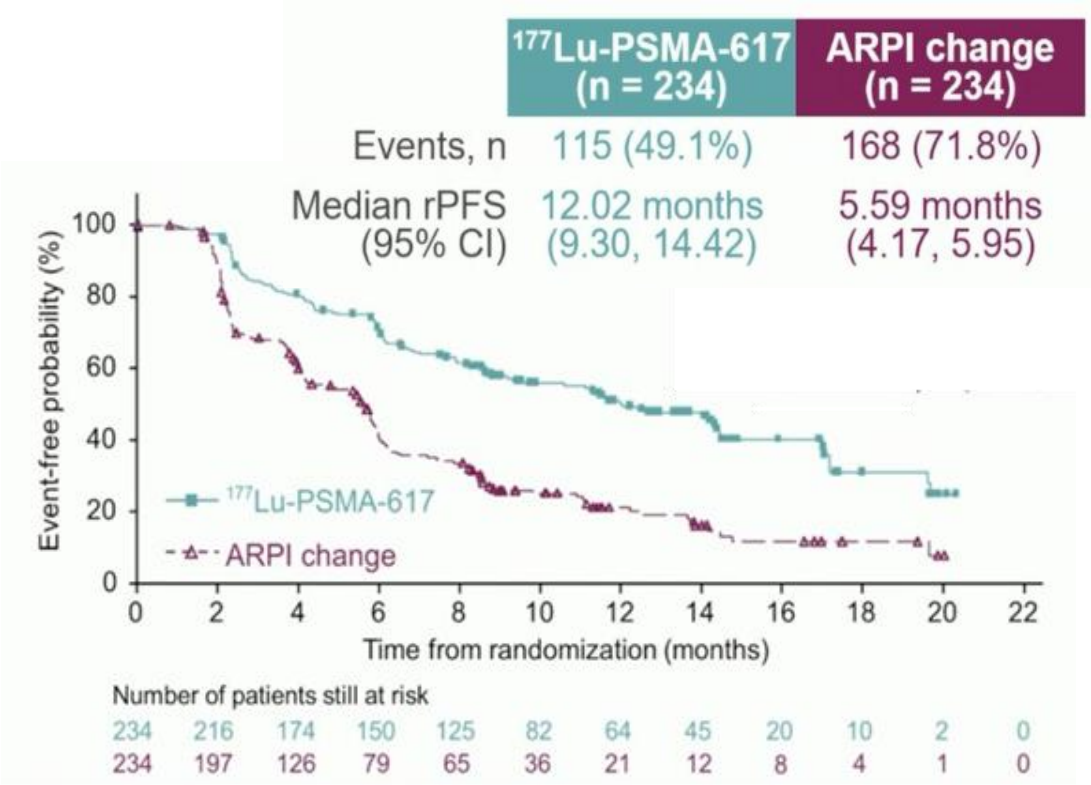
Survival probability	Survival time	95% lower CI	95% upper CI
Treatment 1 (Arm 1)			
0.95	85.15	66.99	129.1
0.9			
0.85			
Treatment 2 (Arm 2)			
0.95	42.82	28.25	75.07
0.9	102.2	82.18	133.1
0.85			

NOTES:

- KM curve states "logHR" but I think it's HR
- Estimated HR=0.56 not match 0.59 exactly but that could be due to my imprecise tracing (could spend more time tracing for improved accuracy)
- User could take the "survival times" CSV file and push it through SAS or R procedure to create KM curves, Cox models, log-rank etc

Case Study #2 – Oncology

Parameter	Competitor	Control
N	234	234
Median rPFS (Months)	11.6	5.59
95% Confidence Interval (CI)	9.3 to 14.19	4.17 to 5.95
Total Number of Events (Censored)	115 (119)	168 (66)



- Events were radiographic disease progression (determined by blinded independent central review per the Prostate Cancer Clinical Trials Working Group 3-modified Response Evaluation Criteria in Solid Tumours v1.1) or death.

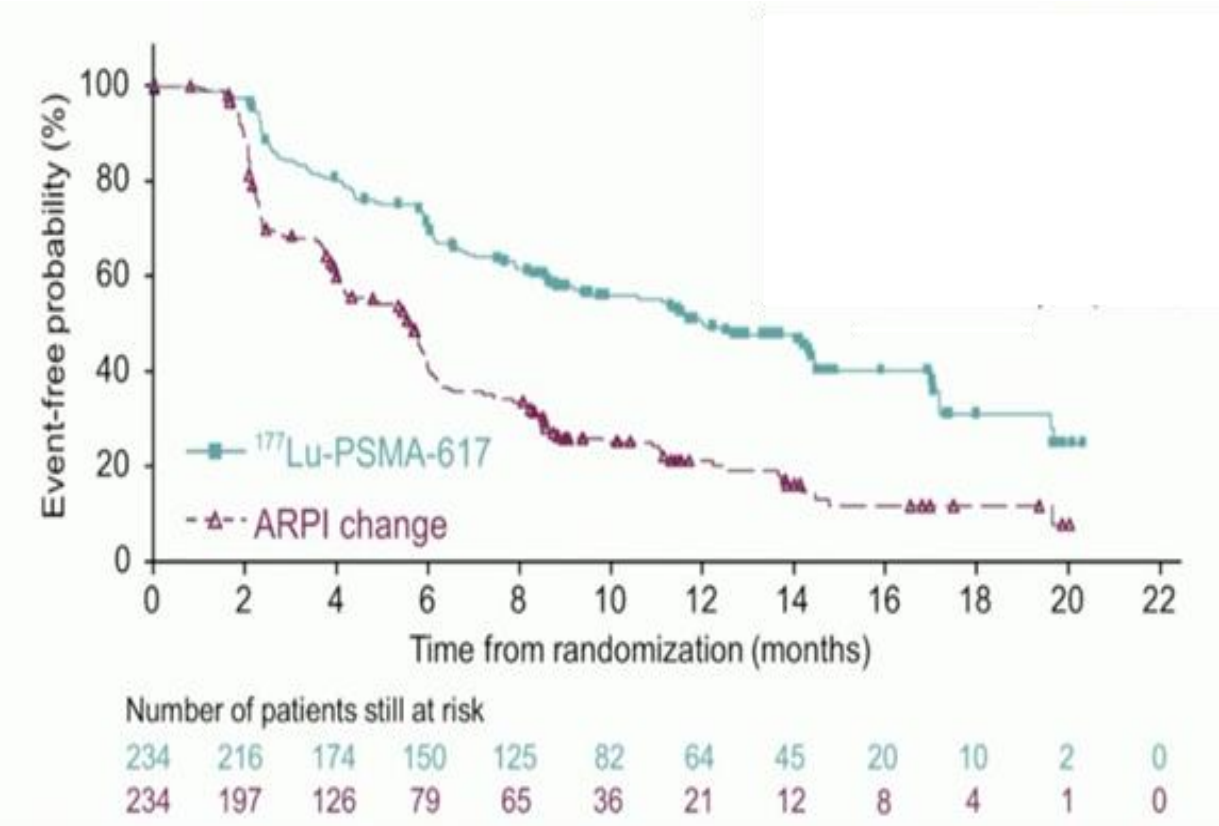
Case Study #2 – Oncology

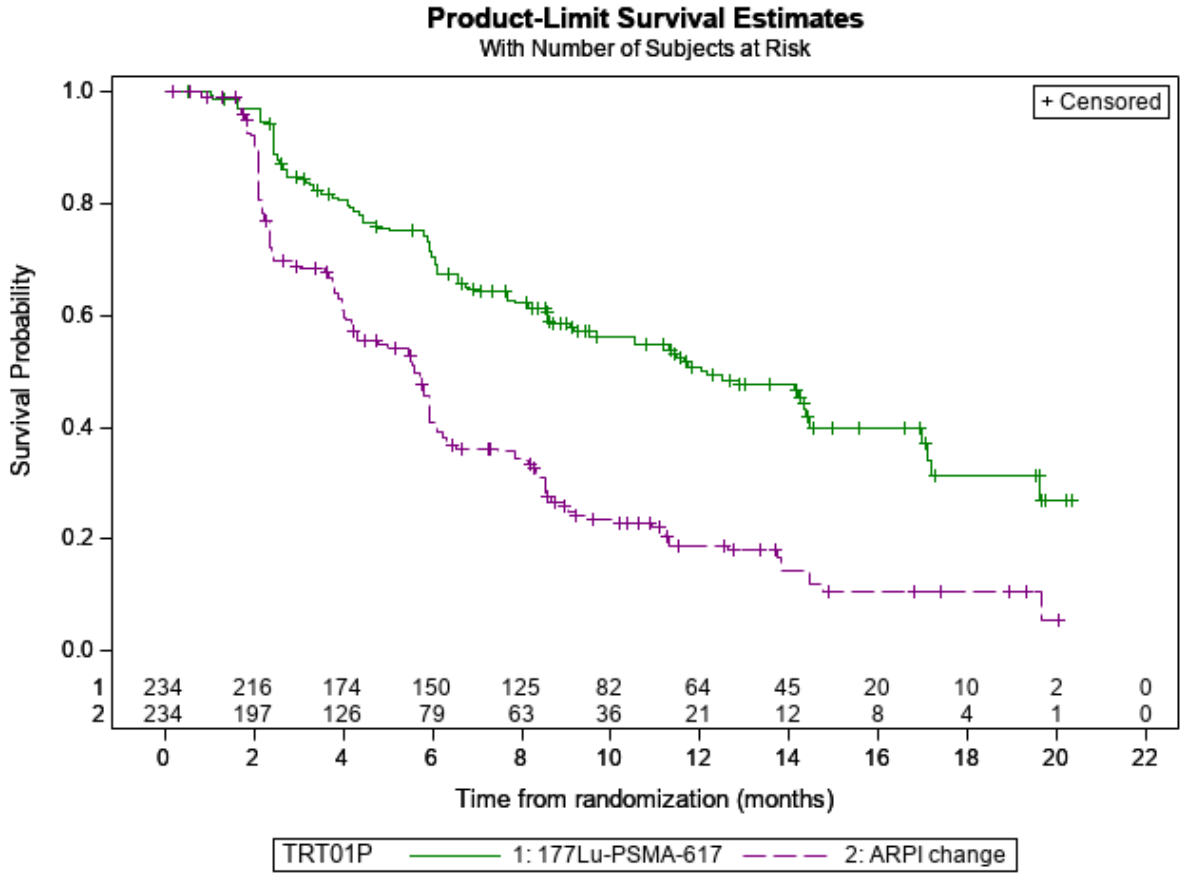
- After the reconstructed IPD Data has been created, this could be converted to ADaM ADTTE format and could be used for comparison at a relevant timepoint whilst the study is ongoing e.g. at 12-months, 18-months

IPDfromKM			ADaM ADTTE					
Survival time	Status	Treatment group	SUBJID	TRT01P	PARAM	PARAMCD	CNSR	AVAL
0.164	0	ARPI	HIST-129	ARPI change	PCWG3 Radiographic Progression-Free Survival (months)	PFSRAD	0	0.164
0.164	0	ARPI	HIST-073	ARPI change	PCWG3 Radiographic Progression-Free Survival (months)	PFSRAD	0	0.164
0.164	0	ARPI	HIST-145	ARPI change	PCWG3 Radiographic Progression-Free Survival (months)	PFSRAD	0	0.164
0.57	0	ARPI	HIST-014	ARPI change	PCWG3 Radiographic Progression-Free Survival (months)	PFSRAD	0	0.57

Case Study #2 – Oncology

- Sas PROC LIFETEST shows accurate digitisation
- Number of patients at risk aligned





Case Study #2 – Oncology

- Sas PROC LIFETEST shows accurate digitisation…

	^{177}Lu-PSMA-617 (n = 234)	ARPI change (n = 234)
Events, n	115 (49.1%)	168 (71.8%)
Median rPFS (95% CI)	12.02 months (9.30, 14.42)	5.59 months (4.17, 5.95)

Summary of the Number of Censored and Uncensored Values

Stratum	TRT01P	Total	Failed	Censored	Percent Censored
1	177Lu-PSMA-617	234	115	119	50.85
2	ARPI change	234	168	66	28.21
Total		468	283	185	39.53

Quartile Estimates

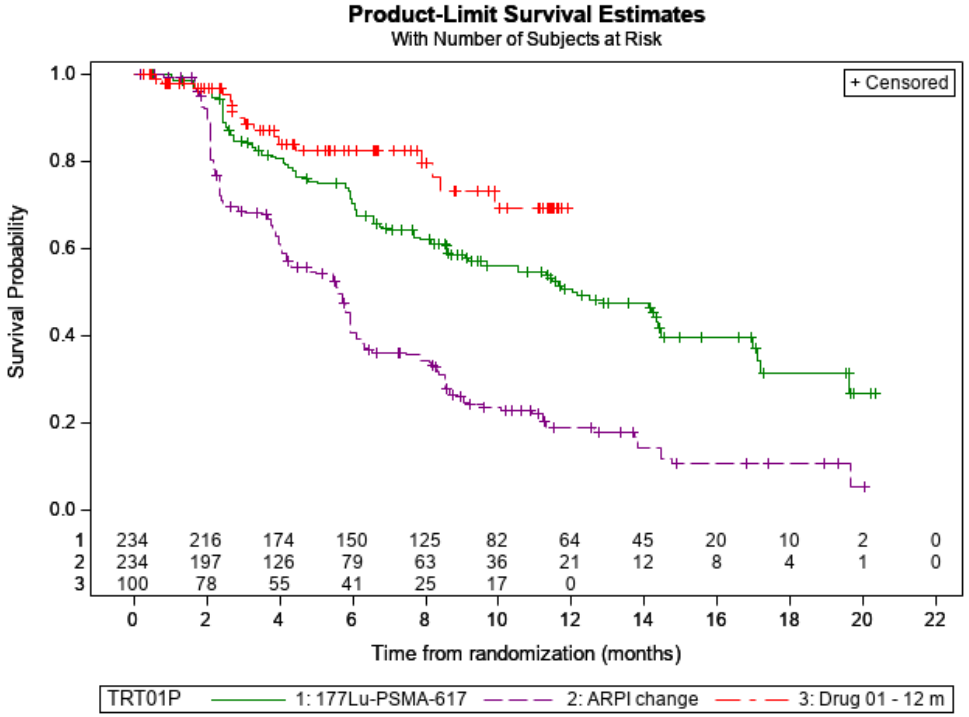
Percent	Point Estimate	95% Confidence Interval		
		Transform	[Lower	Upper)
75	.	LOGLOG	17.0950	.
50	12.1520	LOGLOG	9.5140	14.3820
25	5.7970	LOGLOG	3.9020	6.0570

Quartile Estimates

Percent	Point Estimate	95% Confidence Interval		
		Transform	[Lower	Upper)
75	9.0380	LOGLOG	8.3680	12.6120
50	5.5760	LOGLOG	4.3110	5.9490
25	2.3380	LOGLOG	2.1140	2.8590

Case Study #2 – Oncology

- Digitised data could be used for informal comparisons during study e.g. at 12-months & 18-months after the study starts
- PROC LIFETEST can be used to visually compare rPFS; Proc PHREG for hazard ratios
- The example below uses simulated data for a study with 100 patients
- 12-months



Reference vs. Control (ARPI change)

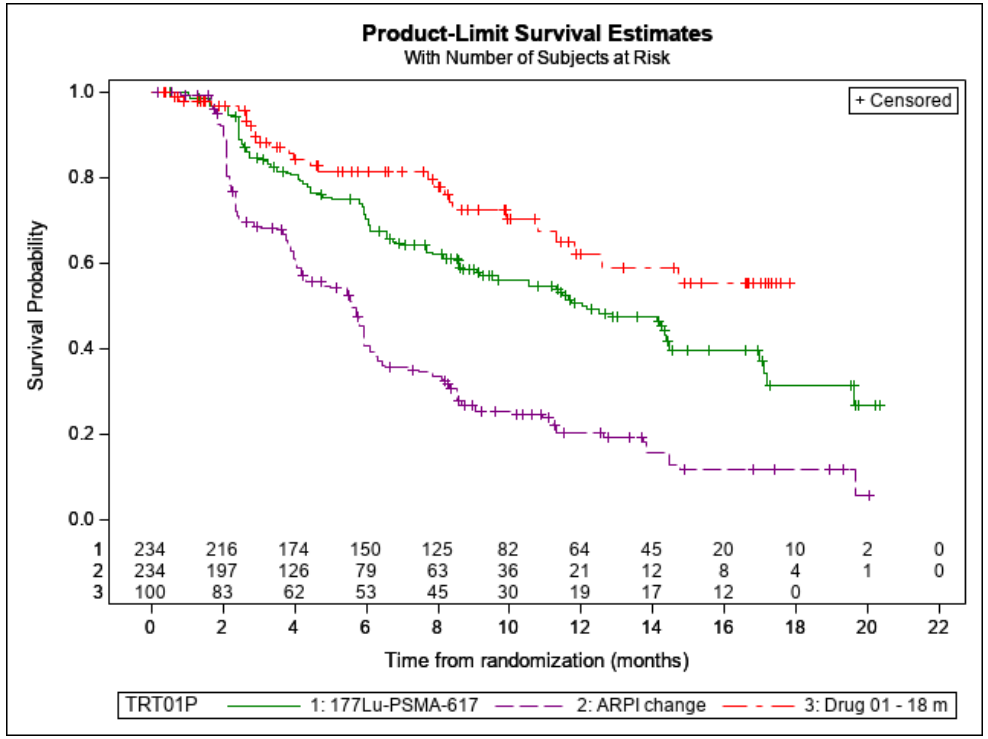
Analysis of Maximum Likelihood Estimates								
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
TRT01P	177Lu-PSMA-617	1	-0.85590	0.12250	48.8193	<.0001	0.425	TRT01P 177Lu-PSMA-617
TRT01P	Drug 01 - 12 m	1	-1.41135	0.25492	30.6515	<.0001	0.244	TRT01P Drug 01 - 12 m

Reference vs. 177Lu-PSMA-617

TRT01P	Drug 01 - 12 m	1	-0.55545	0.26143	4.5141	0.0336	0.574	TRT01P Drug 01 - 12 m

Case Study #2 – Oncology

- 18-months



Reference vs. Control (ARPI change)

Analysis of Maximum Likelihood Estimates								
Parameter		DF	Parameter Estimate	Standard Error	Chi-Square	Pr > ChiSq	Hazard Ratio	Label
TRT01P	177Lu-PSMA-617	1	-0.85777	0.12242	49.0950	<.0001	0.424	TRT01P 177Lu-PSMA-617
TRT01P	Drug 01 - 18 m	1	-1.34578	0.21159	40.4540	<.0001	0.260	TRT01P Drug 01 - 18 m

Reference vs. 177Lu-PSMA-617

TRT01P	Drug 01 - 18 m	1	-0.48800	0.21734	5.0416	0.0247	0.614	TRT01P Drug 01 - 18 m

- Can we say that at both timepoints the example study data had statistically significant better rPFS data compared to the competitor?

Case Study #2 – Oncology

- We couldn’t say this with any confidence, and any decision making should be made with caution.
- Digitisation isn’t perfect, and inaccuracies can occur during digitisation. In general, the results if we repeated the analysis vs. the true IPD would not align perfectly.
- The rhPSMA-617 & ARPI KM curves are based on more mature data than the corresponding 12 (& 18) month timepoints. As such, the actual rhPSMA-617 KM curve at 12 months would have had more censored values earlier in the curve whereas many of those are now PFS events in this more mature datacut.
- A possible mitigation is to digitise every KM curve whenever a competitor publishes it and then use the closest level of maturity as the one you’re interested in.

Conclusions

- Demonstrated method to generate "digitised IPD" that is:
  - Straightforward to implement
  - Zero-cost
  - Reliable / consistent with published results
- Benefits:
  - Enables scenario planning with more complex survival distributions than parametric approaches
  - Can be used by organisations moving into novel disease areas (i.e. no IPD databases)
  - Likely to be quicker than waiting for IPD from Data Sharing portals (Vivli, Yoda etc)

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Conclusions

- Limitations:
  - Will never be as accurate as actual IPD
  - Covariate information unavailable (see Guyot et al, 2012)
  - When comparing "digitised IPD" with current study, keep-in-mind that "digitised IPD" is not contemporaneous (i.e. "historical control") so consider if/how to address biases
- Possible Extensions
  - How might AI help reduce the manual step of digitising?
  - Bootstrapping
  - Could we perform event prediction using digitised data?
  - Other???

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References

- ‘ESMO 2023: PSMAfore Phase 3 Trial of [177Lu]Lu-PSMA-617 in Taxane-Naive Patients with Metastatic Castration Resistant Prostate Cancer’. Accessed 16 April 2025. https://www.urotoday.com/conference-highlights/esmo-2023/esmo-2023-prostate-cancer/147587-esmo-2023-psmafore-phase-3-trial-of-177lu-lu-psma-617-in-taxane-naive-patients-with-mcrpc.html
- Gupta A, Dennis, N. Reconstruction of Individual Patient Data (IPD) from Published Kaplan-Meier Curves Using Guyot’s Algorithm: Step-by-Step Programming in R. PharmaSUG (2023) https://pharmasug.org/download/sde/rtp2023/PharmaSUG-NCSDE_2023-05.pdf
- Guyot, P., Ades, A. E., Ouwens, M. J., & Welton, N. J. (2012). Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Medical Research Methodology*, *12*(1), 9. https://doi.org/10.1186/1471-2288-12-9
- Liu, Na, Yanhong Zhou, and J. Jack Lee. 2021. ‘IPDfromKM: Reconstruct Individual Patient Data from Published Kaplan-Meier Survival Curves’. *BMC Medical Research Methodology*
- Sciurba et al. CHEST (2025) https://journal.chestnet.org/action/showPdf?pii=S0012-3692%2824%2904937-7
- Wassmer G, Pahlke F (2025). rpact: Confirmatory Adaptive Clinical Trial Design and Analysis. R package version 4.2.0. doi:10.32614/CRAN.package.rpact. Available at: https://cran.r-project.org/package=rpact

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